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Health and Environmental Effects Document for Cacodylic Acid

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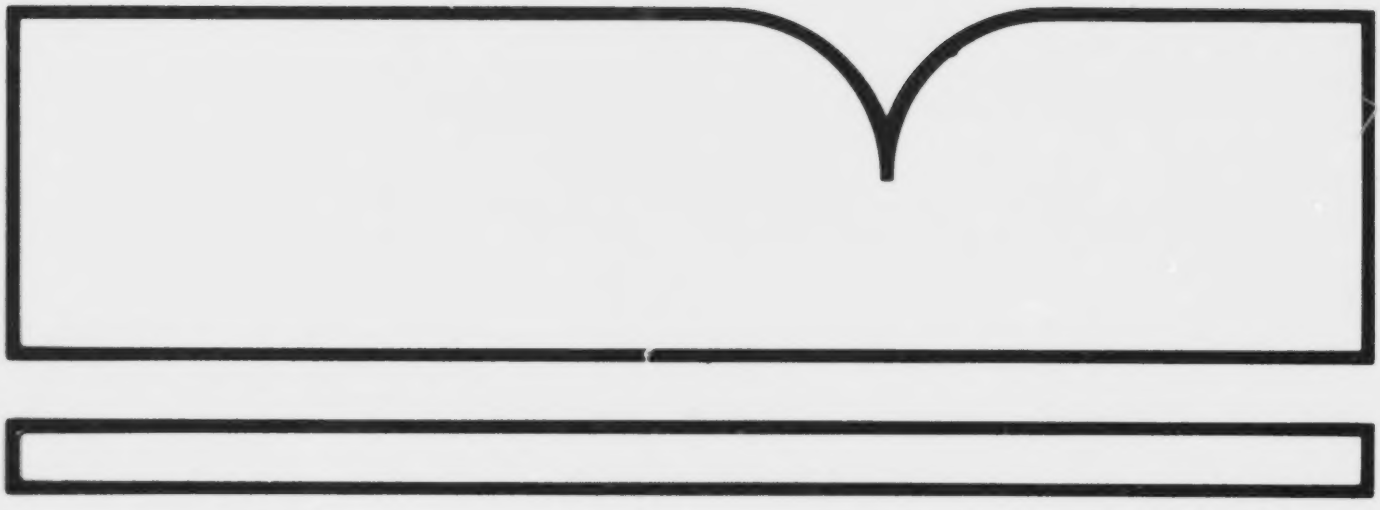

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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR CACODYLIC ACID

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT

Health and Environmental Effects Documents (HEEDS) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference Doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. In the case of suspected carcinogens, RfDs may not be estimated. Instead, a carcinogenic potency factor, or q_1^*, is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively. Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA.

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained for Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval that does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. Instead, a carcinogenic potency factor, or q_1^* (U.S. EPA, 1980), is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984 and 1986a, respectively.

EXECUTIVE SUMMARY

Cacodylic acid is a colorless and odorless solid at ambient temperatures. It is soluble in water and ethanol, but insoluble in ethyl ether (Woolson, 1976; Worthing, 1983). Cacodylic acid is an acid and forms both cationic and anionic compounds. The chemical is produced commercially by the reaction of monosodium methylarsonic acid with methyl chloride and sulfur dioxide at 80°C and 5 psi pressure (Woolson, 1976). It is manufactured in the United States by Vineland Chemical Co., Vineland, NJ, and Drexel Chemical Co., Tunica, MS (SRI, 1987). Data regarding U.S. production volume are not available. It is estimated that a maximum of 4.8 million pounds of cacodylic acid was consumed in the United States in 1987. Cacodylic acid is used as a herbicide, as a desiccant and defoliant for cotton, for killing unwanted trees and thinning forest, and for controlling insects and fungi that attack trees (Woolson, 1976, 1986; Worthing, 1983).

The fate of cacodylic acid in the atmosphere is not well understood. It is likely to be present in the particulate phase of aerodynamic diameter of <4 μm, with a concentration maximum at aerodynamic diameter of 0.5 μm (Tanaka et al., 1984). The oxidation of particulate cacodylic acid by HO• in the atmosphere is likely, but the kinetic data for this reaction, which will allow the estimation of its residence time in air, are not available. Some of the particulate cacodylic acid may be removed by dry and wet deposition. Since this compound is quite stable towards oxidation/reduction (Braman and Foreback, 1973), it may have a long residence time in the air, which will allow it to transport long distances. No data were found in the literature to indicate that cacodylic acid will undergo significant abiotic reaction in water. Biodegradation of cacodylic acid in

water and sediment has been reported, and arsenate is the primary product, although small amounts of arsenite, CO_2 and probably alkylarsines are also formed. The half-life of this compound in water is >1 month (Lemmo et al., 1983; Holm et al., 1980). Significant volatilization of this compound from water is not expected. Sorption onto sediments will cause some cacodylic acid in water to be lost, and the sorption will increase with increase of pH and aluminum and iron content of the sediment; however, the sorption of this compound on sediments is weakest of all the arsenicals (Holm et al., 1980; Lemmo et al., 1983). Bioconcentration of this compound in lower food chain organisms will be significantly higher than in higher food chain organisms. Therefore, significant bioconcentration in edible fish may not occur (Isensee et al., 1973). In aerobic soils, cacodylic acid will undergo biodegradation with the formation of primarily arsenate. The biodegradation rate may depend on the nature of soil, with 90% degradation observed in two soils compared with <5% degradation in another soil (Woolson, 1976; Odanaka et al., 1985a). Conflicting data are available on the degradation products in soils under anaerobic conditions. While one group of researchers (Woolson and Kearney, 1973; Woolson, 1976) reported organoarsenicals as the primary product, another group (Odanaka et al., 1985b) reported inorganic arsenic as the primary product. The sorption of this compound in soil will depend on clay and iron oxide content of the soil, but the sorption capacity may be lower than both arsenate and methylarsonate. Therefore, leaching of this compound particularly from sandy soils may be more prevalent (Wauchope, 1975; Woolson, 1976). No detectable transport or translocation of the herbicide within cotton seeds was observed as a result of application in a cotton field (Mastradone and Woolson, 1983).

Limited monitoring data on the ambient levels of cacodylic acid in any environmental medium are available. The concentration of this compound in air sampled at sites in Japan ranged from 7-270 pg/m³. A seasonal variation in airborne cacodylic acid levels was observed, with maximum levels during summer when the biological activities in aquatic and terrestrial media were maximum (Tanaka et al., 1984; Mukai et al., 1986). The concentrations of this chemical in a few surface waters sampled in the United States were <0.02-1 µg/ℓ, but it was not detected in Tampa tap waters (Braman and Foreback, 1973). Urine samples of presumably unexposed people averaged 15 µg/ℓ, with values as high as 1.8 mg arsenic/ℓ in applicators using monosodium methanearsonate and cacodylic acid. The later level corresponds to an exposure of ≥0.036 mg arsenic/kg bw/24-hour day (Braman and Foreback, 1973; Norris, 1985).

The 96-hour LC_{50}s for mosquitofish and southern toad tadpoles were estimated to be between 100 and 1000 mg/ℓ (Oliver et al., 1966). The 96-hour LC_{50}s for bluegills, amphipods and shrimp were 17, 140 and 135 and 28 mg/ℓ, respectively (Mayer and Ellersieck, 1986). Cockell and Hilton (1988) reported that the NOEC for cacodylic acid in juvenile rainbow trout was ≥1497 µg As/g diet. Mortality was 42.5-97.5% in terrestrial snails given baits containing 1.5-2.4% cacodylic acid.

Uptake of cacodylic acid by organisms in laboratory aquatic ecosystems was greatest in algae, aquatic plants and daphnids, followed by snails, fish and crayfish. Bioconcentration ratios in these organisms ranged from a high of ~1650 for algae and daphnids to ~1-15 for fish and crayfish (Isensee et al., 1973; Schuth et al., 1974). Stary et al. (1982) demonstrated that uptake of cacodylic acid by guppies from water was neglible after a few days of exposure and that 95% of the tissue residues from ingested cacodylic acid

was depurated within hours. Calculated BCFs estimated from log K_{ow} and water solubility were <1, suggesting that cacodylic acid was not likely to accumulate in the tissues of aquatic organisms.

Algal productivity was reduced by 50% in the presence of 55.3 ppm cacodylic acid for 48 hours (Oliver et al., 1966). Reproduction in brown algae was inhibited by 35 mM of the sodium salt of cacodylic acid (Roederer, 1986).

Field studies revealed low to moderate effects on vegetation from three terrestrial communities exposed to 2 lbs/acre of cacodylic acid. Treatment levels of 30 lbs/acre were highly detrimental to the survival of vegetation in those communities (Oliver et al., 1966).

Cacodylic acid appears to be asorbed rapidly and virtually completely from the respiratory tract of intratracheally treated rats, with a half-time of 2.2 minutes. Gastrointestinal absorption in rats is considerably slower, with an estimated half-time of 248 minutes (Stevens et al., 1977). Excretion data in rats (Stevens et al., 1977), hamsters (Yamauchi and Yamamura, 1984; Marafante et al., 1987) and mice (Marafante et al., 1987) indicate that GI absorption ranges from ~60-70% in these species. Urinary excretion data in humans (Marafante et al., 1987; Buchet et al., 1981) suggest a GI absorption factor for humans of ~80%.

Distribution data obtained from rats treated intravenously with high (200 mg/kg) and low (33 µg) doses indicate that the rat RBC has an affinity for cacodylic acid (Stevens et al., 1977). Among other tissues, highest concentrations were found in the liver > kidney > lung > spleen > brain. The magnitude of the dose had no effect on tissue distribution. Plasma elimination was triphasic, with a terminal half-life of 3.42 hours.

Tissue distribution appeared to be similar in hamsters, except that the hamster RBC did not appear to have a particular affinity for cacodylic acid (Yamauchi and Yamamura, 1984).

The metabolism of cacodylic acid has been studied by quantifying its metabolites in tissue, expired air and excreta of treated rats, mice, hamsters and humans (Stevens et al., 1977; Yamauchi and Yamamura, 1984; Marafante et al., 1987). Excretion data in hamsters, mice and humans suggest that metabolism is not nearly as important as excretion in the elimination of cacodylic acid (Marafante et al., 1987). Demethylation to methylarsonic acid, inorganic arsenic and carbon dioxide appears to be a minor metabolic pathway (Yamauchi and Yamamura, 1984; Stevens et al., 1977). The most important biotransformation pathway appears to be methylation to a trimethyl compound, probably to a trimethylarsine oxide conjugate (Yamauchi and Yamamura, 1984; Marafante et al., 1987). Complexation with thio-containing compounds may be an intermediate step in the formation of trimethylarsine oxide.

Excretion of a parenteral dose is primarily through the kidney, with minor amounts expired as CO_2 and excreted through the bile (Stevens et al., 1977; Marafante et al., 1987). Fecal excretion of an oral dose probably represents largely unabsorbed compound. A plasma half-life in rats of 3.42 hours was estimated for the terminal phase of a triphasic decay function (Stevens et al., 1977). In hamsters and mice, urinary and fecal excretion together accounted for 97.5 and 96.8% of an oral dose after 48 hours, suggesting that excretion in these species is fairly rapid (Marafante et al., 1977). In humans, ~80% of an oral dose was recovered from the urine within 3 days of treatment (Marafante et al., 1987; Buchet et al., 1981).

Oral LD_{50} values in rats range from 644-1433 mg/kg, with little apparent difference in magnitude regardless of age or gender (see Table 6-1). Inhalation and intraperitoneal single exposure data indicate little difference in the sensitivity of rats compared with mice. Intraperitoneal LD_{50} values in both species ranged from 500-1000 mg/kg. In a 20-day dietary study using rats, testicular effects were observed at 180 mg/kg bw/day, but not at 140 mg/kg bw/day (Nees, 1960). A dietary concentration of 184 ppm was a NOEL in rats in a 30- to 90-day dietary study (Nees, 1968) and 30 ppm was a NOEL in a 90-day study using dogs (Derse, 1968). It is not clear whether the testis was examined in these longer-term studies.

Data regarding the toxicity of cacodylic acid in humans were not located; however, workers applying arsenic-containing silvicides had higher urinary concentrations of arsenic compounds, including cacodylic acid, than did nonexposed controls. The levels of cacodylic acid in the urine did not appear to rise with increased duration of exposure. Near normal levels were observed on Monday mornings.

Cacodylic acid did not yield evidence of carcinogenicity in an 18-month gavage/dietary study in which mice were exposed to 46.4 mg/kg/day by gavage from 7-28 days of age and 121 ppm in the diet after 28 days of age (BRL, 1968; Innes et al., 1969). In a different BRL (1968) experiment with mice, a single subcutaneous injection at 464 mg/kg of cacodylic acid in distilled water did not produce a significant increase in tumor incidence compared with controls. A drinking water study produced equivocal evidence that cacodylic acid may promote liver tumors in partially hepatectomized rats initiated with DENA (Johansen et al., 1984). Results of mutagenicity testing were mixed. Tests in prokaryotes (Simmon et al., 1977; Jones et al., 1984; Andersen et al., 1972) and Drosophilia (Ramel and Magnusson,

1979; Valencia, 1981) were negative, but tests in Saccharomyces were positive (Simmon et al., 1977; Jones et al., 1984). Mixed results were obtained in various mammalian test systems (Simmon et al., 1977; Jones et al., 1984; Taylor et al., 1984). The compound is not scheduled for testing by the NTP (1988).

Developmental toxicity studies (Rogers et al., 1981; Kavlock et al., 1985; Chernoff and Kavlock, 1982) suggest that rats are more sensitive than mice. In a gavage study using rats, 40 mg/kg/day was associated with retarded maternal weight gain, reduced fetal body weights and retarded ossification (Rogers et al., 1981). An increased incidence of irregular palatine rugae was observed at 30 mg/kg/day. There were no significant effects at 15 mg/kg/day. In mice treated by gavage, 200 mg/kg/day resulted in adverse body weight effects on both the dam and the fetus; 400 mg/kg/day resulted in an increased incidence of cleft palate (Rogers et al., 1981).

An interim RfD of 0.03 mg/kg/day was derived for subchronic oral exposure to cacodylic acid based on the NOEL of 9.2 mg/kg/day for rats in the 90-day dietary study by Nees (1968). An interim RfD of 0.003 mg/kg/day was derived from the same data for chronic oral exposure. The RfD values are well below the line for adverse effects in a dose/duration-response plot of the oral toxicity data. An RQ of 1000 pounds was derived based on mild teratogenic effects in rats in a developmental toxicity study (Rogers et al., 1981). Based on inadequate data concerning the carcinogenicity of cacodylic acid, it was assigned to EPA Group D, not classifiable as to human carcinogenicity. A cancer-based RQ was not derived.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CBI	Confidential Business Information
CS	Composite score
DENA	Diethylnitrosamine
DNA	Deoxyribonucleic acid
FEL	Frank-effect level
GI	Gastrointestinal
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted concentration levels)
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOCEL	No-observed-carcinogenicity-effect level
NOEC	No-observed-effect concentration
NOEL	No-observed-effect level
PEL	Permissible exposure level
ppm	Parts per million
RBC	Red blood cell
RfD	Reference dose
RQ	Reportable quantity

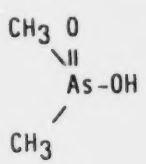
LIST OF ABBREVIATIONS (cont.)

RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TMA	Trimethylarsine
TMAO	Trimethylarsine oxide

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The common chemical name for cacodylic acid is dimethylarsinic acid. It is also known as hydroxydimethylarsine oxide. Some of the common trade names of this chemical are Ansar 138, Bolls-eye, Phytar 138 and Silvisar 510 (HSDB, 1988; Worthing, 1983). The structure, molecular formula, molecular weight and CAS Registry number for cacodylic acid are as follows:



Molecular formula: $C_2H_7AsO_2$

Molecular weight: 138.01

CAS Registry Number: 75-60-5

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Cacodylic acid is a colorless and odorless solid at ambient temperature; it is soluble in water and ethanol, but insoluble in ethyl ether (Worthing, 1983; Woolson, 1976). Some of the relevant physical properties of this chemical are listed below:

Melting point:	200°C	Woolson, 1976
Boiling point:	not available	
Density:	not available	
Water solubility:	667,000 mg/ℓ at 20-25°C	Woolson, 1976
Vapor pressure:	not available	
Log K_{ow}:	-1.78 (estimated from regression equation)	Lyman et al., 1982
pKa at 25°C:	6.29	Wauchope, 1976

As indicated by its pKa value, this compound is an acid and forms the sodium salt with NaOH at about neutral pH (Worthing, 1983). Since cacodylic acid is amphoteric (Lemmo et al., 1983), it can form both cationic and anionic compounds. Cacodylic acid undergoes two main kinds of reactions, one with acids and the other with metal salts; for example, it reacts with HI to form dimethyl arsenic iodide. Details of these reactions are available in a review article by Lemmo et al. (1983). It is quite stable towards oxidation/reduction, and only strong oxidizing and reducing agents are required for its decomposition (Worthing, 1983; Braman and Foreback, 1973).

1.3. PRODUCTION DATA

Cacodylic acid is made commercially by the reaction of monosodium methylarsonic acid with methyl chloride and sulfur dioxide at 80°C and 5 psi pressure (Woolson, 1976). It can also be made by the alkylation of disodium methanearsonate with methyl chloride, followed by hydrolysis of the product with HCl (HSDB, 1988). According to the Directory of Chemical Producers (SRI, 1987), Drexel Chemical Co, Tunica, MS, and Vineland Chemical Co., Vineland, NJ, are the current producers of cacodylic acid in the United States. USITC (1987) lists only the former company as a manufacturer of this chemical in the United States in 1986. It was reported that 2 million pounds of cacodylic acid was produced in the United States in 1971 (Lewis and Lee, 1976). The current U.S. production volume of cacodylic acid is not available. The total consumption of arsenic and compounds in 1987 was 50.7 million pounds (expressed as arsenic); 19% of the total consumption was used for agricultural chemicals (USDI, 1988). If it is assumed that a maximum of 50% of the total agricultural usage was in the form of cacodylic acid (Woolson, 1976), a maximum of 4.8 million pounds of this chemical was

consumed in the United States in 1987. Technical grade cacodylic acid is 65% pure and contains NaCl as one of the impurities (Worthing, 1983).

1.4. USE DATA

Cacodylic acid is used as a nonselective postemergent herbicide for weed control, for lawn renovation, as a desiccant and defoliant for cotton, for killing unwanted trees by injection, for thinning forests, and for controlling insects and fungi that attack trees (Woolson, 1976, 1986; Worthing, 1983).

1.5. SUMMARY

Cacodylic acid is a colorless and odorless solid at ambient temperatures. It is soluble in water and ethanol, but insoluble in ethyl ether (Woolson, 1976; Worthing, 1983). Cacodylic acid is an acid and forms both cationic and anionic compounds. The chemical is produced commercially by the reaction of monosodium methylarsonic acid with methyl chloride and sulfur dioxide at 80°C and 5 psi pressure (Woolson, 1976). It is manufactured in the United States by Vineland Chemical Co., Vineland, NJ, and Drexel Chemical Co., Tunica, MS (SRI, 1987). Data regarding U.S. production volume are not available. It is estimated that a maximum of 4.8 million pounds of cacodylic acid was consumed in the United States in 1987. Cacodylic acid is used as a herbicide, as a desiccant and defoliant for cotton, for killing unwanted trees and thinning forest, and for controlling insects and fungi that attack trees (Woolson, 1976, 1986; Worthing, 1983).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

The fate of cacodylic acid in the atmosphere is not well understood. Because cacodylic acid is an ionic compound, it is not expected to volatilize significantly from aquatic or terrestrial media. As a result of its use in agricultural and forest lands, however, it is likely to be transported as aerosols to the atmosphere. A second process that may transport aquatic and terrestrial arsenic from cacodylic acid to the atmosphere is its conversion to volatile dimethyl and trimethyl arsines by both bacteria and fungi that may be present in the natural ecosystem (Cox and Alexander, 1973; Wong et al., 1977). Methyl arsines at concentrations >0.05-0.10 ppm are very unstable in air and are oxidized rapidly. At low concentrations, methyl arsines are more stable and may be transported from the source before being oxidized in air (Lemmo et al., 1983). The oxidation products of trimethyl arsines in air have been identified as trimethylarsine oxide and cacodylic acid (Parris and Brinckman, 1976). The oxidation of particulate cacodylic acid by HO• in air is likely. This is supported by the fact that a very slow oxidation of this compound to arsenate has been observed in model aquatic systems (Holm et al., 1980). Rate constants for reactions of cacodylic acid with the oxidants present in the atmosphere are not available.

The fate of atmospheric cacodylic acid may be partially assessed from the monitoring data. An abstract of a Japanese publication (Tanaka et al., 1984) reported that cacodylic acid was found in the particulate phase but not in the gas phase. All the organic arsenic was present in particles of aerodynamic diameter <4 μm, with a concentration maximum at 0.5 μm. Therefore, cacodylic acid in the atmosphere is expected to be present as inhalable particles. Besides oxidation, some of the particulate cacodylic acid may be removed from the atmosphere by dry and wet deposition.

2.2. WATER

The fate of cacodylic acid in water at environmental concentration levels with respect to abiotic reactions, such as hydrolysis, oxidation and reduction, and photolysis has not been well studied. It is known that this compound will not oxidize chemically under mild oxidation conditions (Braman and Foreback, 1973), nor does it contain any functional group that is amenable to hydrolysis. Therefore, it could be resistant to abiotic reactions in water. The biotic oxidation, reduction and mineralization of cacodylic acid in water was reported by a few authors. In a model aquatic ecosystem study, cacodylic acid formed arsenate, arsenite, CO_2 and probably alkylarsine. Arsenate was the predominant form after 59 days (Lemmo et al., 1983); however, the conversion rates of cacodylic acid to arsenate in model aquatic systems was estimated at 0.067-0.404% per day. If first-order kinetics is assumed, the half-life of the oxidation process is 6-35 months (Holm et al., 1980). In a sediment incubation experiment, the biodegradation of cacodylic acid proceeded with the formation of inorganic arsenic. The rate of cacodylic acid degradation could be explained almost exclusively on the basis of arsenate formation (Holm et al., 1980). The degradation half-life was ~30 days. According to Andreae (1979), the uptake of arsenate from the photic region of the ocean by plankton is followed by conversion of inorganic arsenate to methylated species by an unknown mechanism(s). Biological demethylation of methylarsenicals to inorganic arsenate also occurs by unknown mechanisms. The concentrations of arsenic species in water are controlled primarily by the relative rates of biological reactions, superimposed on physical transport processes. Biomethylation of arsenic does not occur in the interstitial waters of aerobic and anaerobic sediments (Andreae, 1979).

The loss of cacodylic acid from direct volatilization will be insignificant because the compound is ionic. (The loss of small amounts of the compound from volatilization of methyl arsines formed as a result of biotransformation will occur.) Some loss of cacodylic acid from sorption onto sediments will occur. Based on a water solubility value given in Section 1.2. and the regression equation, log K_{oc} = -0.55 log S + 3.64 (Lyman et al., 1982), a K_{oc} value of 3 can be estimated. This would predict a negligible sorption of cacodylic acid on sediments; however, the sorption equation is not valid for cacodylic acid where the sorption is due primarily to ionic interaction. The sorption behavior of cacodylic acid on soils and sediments was found to depend on the clay content, more specifically, the aluminum and iron content of the clay, and on the pH of the medium. The dependence on pH is probably due to the dependence of the dissociation equilibrium of cacodylic acid on the pH (Wauchope and McDowell, 1984). Sorption of arsenicals on sediments follows a Langmuir isotherm pattern. Among the arsenicals, arsenate is sorbed most strongly, followed by monomethyl arsonic acid, arsenite and cacodylic acid. Therefore, the sorption of cacodylic acid on sediments is weakest of all the arsenicals (Holm et al., 1980; Lemmo et al., 1983).

The bioaccumulation of alkyl arsenicals was studied in a model ecosystem (Isensee et al., 1973). The BCFs in dried tissues were 1635 for algae, Oedogonium cardiacum; 1658 for daphnia, Daphnia magna; and 21 for fish, Gambusia affinis, indicating that lower food chain organisms bioconcentrated more cacodylic acid than did higher food chain organisms.

2.3. SOIL

The fate of cacodylic acid in soil has been studied more extensively than its fate in air and water. Under aerobic conditions, cacodylic acid

primarily degrades by two mechanisms, one leading to the formation of arsenate and the other to volatile organic arsenicals, probably dimethylarsine or an oxide. A small amount of cacodylic acid may be lost as a result of complete mineralization to CO_2 and arsenate (Woolson, 1976). Odanaka et al. (1985a), however, reported almost exclusive detection of inorganic arsenic (species not identified) from aerobic degradation of two soils. Evolution of volatile arsenic compounds was found to be a relatively minor route. The rate of aerobic degradation was also found to depend on soil type. For example, the aerobic degradation of cacodylic acid was ~90% in 6 weeks in two soils, but was <5% in another soil (Odanaka et al., 1985a). Whether the difference in the degradation rate is due to the difference in some physical characteristics of the soil or to the presence of a higher number of degrader/acclimatized microorganisms is not clear. Under anaerobic conditions, one group of authors reported volatile organoarsenicals as the primary degradation product in soil (Woolson and Kearney, 1973; Woolson, 1976), while another group (Odanaka et al., 1985b) reported inorganic arsenic as the primary product. In the experiments of Woolson and Kearney (1973), the anaerobic degradation of cacodylic acid in three soils produced on the average 61% volatile organic-arsenicals in 24 weeks. Odanaka et al. (1985b), however, reported almost 90% degradation of cacodylic acid to inorganic arsenic in two flooded soils and almost no degradation in a third soil after 6 weeks of incubation. Neither group reported detection of arsine gas from the degradation of cacodylic acid in soils.

The sorption of cacodylic acid by soil was found to depend on the clay and iron oxide content of the soil; however, the sorption capacity of cacodylate is lower than both arsenate and methylarsonate (Wauchope, 1975).

Cacodylic acid can form insoluble compounds with aluminum in soil and a certain part of sorbed cacodylic acid may remain fixed in soil in an occluded form (Woolson, 1976). Leaching of this compound from field soils, particularly from sandy soils, may be more prevalent than the leaching of arsenate and methylarsonate.

The level of cacodylic acid in cotton seeds collected between the second day and harvesting time following application of the herbicide was nearly at the preapplication level. It was concluded that there was no detectable transport or translocation of the herbicide within the plant as a result of application (Mastradone and Woolson, 1983).

2.4. SUMMARY

The fate of cacodylic acid in the atmosphere is not well understood. It is likely to be present in the particulate phase of aerodynamic diameter of <4 μm, with a concentration maximum at aerodynamic diameter of 0.5 μm (Tanaka et al., 1984). The oxidation of particulate cacodylic acid by HO• in the atmosphere is likely, but the kinetic data that will allow the estimation of its residence time in air for this reaction are not available. Some of the particulate cacodylic acid may be removed by dry and wet deposition. Since this compound is quite stable towards oxidation/reduction (Braman and Foreback, 1973), it may have a long residence time in the air, which will allow it to transport long distances. No data were found in the literature to indicate that cacodylic acid will undergo significant abiotic reaction in water. Biodegradation of cacodylic acid in water and sediment has been reported, and arsenate is the primary product, although small amounts of arsenite, CO_2 and probably alkylarsines are also formed. The half-life of this compound in water is >1 month (Lemmo et al., 1983; Holm et al., 1980). Significant volatilization of this compound from

water is not expected. Sorption onto sediments will cause some cacodylic acid in water to be lost, and the sorption will increase with increase of pH and aluminum and iron content of the sediment; however, the sorption of this compound on sediments is weakest of all the arsenicals (Holm et al., 1980; Lemmo et al., 1983). Bioconcentration of this compound in lower food chain organisms will be significantly higher than in higher food chain organisms. Therefore, significant bioconcentration in edible fish may not occur (Isensee et al., 1973). In aerobic soils, cacodylic acid will undergo biodegradation with the formation of primarily arsenate. The biodegradation rate may depend on the nature of soil, with 90% degradation observed in two soils compared with <5% degradation in another soil (Woolson, 1976; Odanaka et al., 1985a). Conflicting data are available on the degradation products in soils under anaerobic conditions. While one group of researchers (Woolson and Kearney, 1973; Woolson, 1976) reported organoarsenicals as the primary product, another group (Odanaka et al., 1985b) reported inorganic arsenic as the primary product. The sorption of this compound in soil will depend on clay and iron oxide content of the soil, but the sorption capacity may be lower than both arsenate and methylarsonate. Therefore, leaching of this compound particularly from sandy soils may be more prevalent (Wauchope, 1975; Woolson, 1976). No detectable transport or translocation of the herbicide within cotton seeds was observed as a result of application in a cotton field (Mastradone and Woolson, 1983).

3. EXPOSURE

Limited monitoring data on the ambient levels of cacodylic acid in any environmental medium are available. More than 99% of the arsenicals in the atmosphere over various sites in Japan was reported to be present as inorganic arsenic. The concentration of organic arsenicals in air particulate matter at these sites was 30-270 pg/m^3. Most of the organic arsenic was in the form of cacodylic acid, and no gaseous organic arsenic was found in the atmosphere. Organic arsenicals were present as fine particles, with a concentration peak at an aerodynamic diameter of 0.5 μm (Tanaka et al., 1984). The levels of cacodylic acid in the air over an unpolluted island and over a rural inland area in Japan were in the range of 7 and 71 pg arsenic/m^3. A seasonal variation in airborne cacodylic acid was also observed, with maximum levels during summer when the biological activity on aquatic and terrestrial media were maximum, and minimum levels during the winter (Mukai et al., 1986).

The concentrations of cacodylic acid in a wide range of fresh natural waters including lakes, rivers and ponds in and around Tampa, FL, were in the range <0.02-0.62 μg/ℓ. Saline waters at several locations along the shores of Tampa Bay contained 0.2-1.0 μg/ℓ of cacodylic acid. The concentration of this chemical in well water at a remote camping site near Withlacoochee River in Florida was 0.2 μg/ℓ. No cacodylic acid was detected (detection limit of 0.02 μg/ℓ) in Tampa tap waters (Braman and Foreback, 1973). Lake, river and pond waters from the Moira River area in Ontario, Canada, which flows through an abandoned smelter (still emitting high levels of arsenic from its watershed), contained 2.3-3.3 μg/ℓ of cacodylic acid (Wong et al., 1977).

Cacodylic acid levels in other media have been reported. Samples of seashells, bird eggshells and a sedimentary rock contained unreported amounts of the compound (Braman and Foreback, 1973). Urine samples of (presumably unexposed) humans contained an average 15 µg/ℓ of cacodylic acid, constituting an average of 66% of the total urinary arsenic excretion (Braman and Foreback, 1973). In forestry workers, the urinary cacodylic acid level in 11 weeks ranged from 24-172 µg/24 hours compared with a range of 26-73 µg/24 hours during the same period for nonexposed workers. Based on this analysis, it was concluded that urinary excretion of arsenic correlates well with and constitutes an index of exposure; blood arsenic levels, however, correlated poorly with exposure (Wagner and Weswig, 1974). The same conclusion was reached by Norris (1985), who detected levels of arsenic as high as 1.8 mg/ℓ in urine of exposed forestry workers, corresponding to an exposure of $\geq$0.036 mg arsenic/kg bw/24-hour day in applicators of monosodium methanearsonate and cacodylic acid.

3.1. SUMMARY

Limited monitoring data on the ambient levels of cacodylic acid in any environmental medium are available. The concentration of this compound in air sampled at sites in Japan ranged from 7-270 pg/m^3. A seasonal variation in airborne cacodylic acid levels was observed, with maximum levels during summer when the biological activities in aquatic and terrestrial media were maximum (Tanaka et al., 1984; Mukai et al., 1986). The concentrations of this chemical in a few surface waters sampled in the United States were <0.02-1 µg/ℓ, but it was not detected in Tampa tap waters (Braman and Foreback, 1973). Urine samples of presumably unexposed people

averaged 15 µg/ℓ, with values as high as 1.8 mg arsenic/ℓ in applicators using monosodium methanearsonate and cacodylic acid. The later level corresponds to an exposure of ≥0.036 mg arsenic/kg bw/24-hour day (Braman and Foreback, 1973; Norris, 1985).

4. ENVIRONMENTAL TOXICOLOGY

4.1. AQUATIC TOXICOLOGY

4.1.1. Acute Toxic Effects on Fauna. Oliver et al. (1966) assessed the toxicity of cacodylic acid to mosquito fish, Gambusia affinis, and southern toad tadpoles, Bufo terrestris. Tests were conducted in 6 ℓ Erlenmeyer flasks each containing 4 ℓ of test solution with 30 fish and 50 tadpoles in each flask. Treatments were not replicated. No mortality was reported among fish and tadpoles exposed to 100 ppm cacodylic acid after 48-72 hours, and 100% mortality was reported among fish and tadpoles exposed to 1000 ppm cacodylic acid after 48 hours.

Mayer and Ellersieck (1986) reported the results of studies assessing the acute toxicity of cacodylic acid to one species of fish and two crustacean species. Bluegill sunfish, Lepomis macrochirus, were exposed to 100% technical material of cacodylic acid in soft water (44 mg/ℓ as $CaCO_3$) at 18°C under static conditions. Under these conditions, the 24- and 96-hour LC_{50}s (and 95% confidence limits) for bluegills were 21 (19-23) and 17 mg/ℓ (15-19), respectively. Studies with the amphipod, Gammarus fasciatus, were conducted under static conditions at 15°C in both soft (44 mg/ℓ as $CaCO_3$) and hard water (272 mg/ℓ as $CaCO_3$). The 96-hour LC_{50}s (with 95% confidence limits) for amphipods under these conditions were 140 (40-486) and 135 mg/ℓ (80-227), respectively. The 96-hour LC_{50} (with 95% confidence limits) for shrimp, Palaemonetes kadiakensis, exposed to cacodylic acid at 21°C in hard water (272 mg/ℓ as $CaCO_3$) under static conditions was 28 mg/ℓ (14-58).

4.1.2. Chronic Effects on Fauna.

4.1.2.1. TOXICITY -- Cockell and Hilton (1985) reported that cacodylic acid did not produce sublethal responses in rainbow trout, Salmo

gairdneri, fed 1600 ppm in the diet over an 8-week period. Sublethal endpoints monitored included feed refusal, growth depression and impaired feeding efficiency. Cockell and Hilton (1988) reported a dose-response relationship between the cacodylic acid exposure rate and the levels of carcass arsenic residues. Residue levels rose from 3.0-11.4 µg As/g carcass as the level of arsenic in the diet increased from 163-1497 µg As/g diet. The investigators also reported that the NOEC for cacodylic acid in juvenile rainbow trout was ≥1497 µg As/g diet.

4.1.2.2. BIOACCUMULATION/BIOCONCENTRATION -- Isensee et al. (1973) monitored the uptake of cacodylic acid by a variety of species in a static laboratory aquatic ecosystem. Experiments were conducted in 4 ℓ of test solution in all glass aquariums at 22±1°C. Test organisms included a filamentous algae, Oedogonium cardiacum, daphnids, Daphnia magna, snails, Physa sp., mosquitofish, Gambusia affinis, and a variety of diatoms, protozoa and rotifers. Organisms other than fish were allowed to adjust to tank conditions for 5 days before introducing the test material. Fish were added 29 days after the addition of test material. The study duration was 32 days. Bioaccumulation ratios were based on the levels of ^{14}C in environmental samples and calculated from the ratio of cpm/mg tissue to cpm/mg of solution. Bioconcentration ratios for algae, daphnids, snails, and fish were 1635, 1658, 110-419 and 21, respectively.

Schuth et al. (1974) monitored the uptake of cacodylic acid by a variety of species in static laboratory aquatic microecosystems for 20 days. Three different soils were treated with 15 mℓ of an aqueous solution containing 19 µCi of [^{14}C]cacodylic acid and 244 mg of unlabeled cacodylic acid and mixed with an additional 10.9 kg of the same soil. After treatment, 11.4 kg of soil was layered on the bottom of separate 110-l all-glass aquarium

tanks, flooded with 80 ℓ of distilled water and allowed to equilibrate for 1 week. Aeration was initiated when organisms were added to the tanks. Organisms included catfish, Ictalurus punctatus, crayfish, Procambarus clarki, daphnids, D. magna, snails, Physa sp., filamentous algae, O. cardiacum, and duckweed, Lemna minor. Concentrations of cacodylic acid in organisms and environmental samples were determined by analysis for ^{14}C and arsenic by a variety of methods.

The investigators reported bioconcentration ratios of cacodylic acid based on ^{14}C (concentration in tissues/concentration in water) ranging from 80-298, 52-88, 51-147, 22-26, 0.8-2.8 and 0.5-2.0 for algae, duckweed, daphnids, snails, catfish and crayfish soft tissue, respectively. Estimates of bioconcentration ratios based on levels of arsenic in tissues and water samples were comparable with those determined by ^{14}C. Bioconcentration ratios calculated for these organisms in a second experiment were much higher than previously observed. Investigators reported bioconcentration ratios of cacodylic acid based on ^{14}C for the second 20-day study ranging from 163-27,000, 174-1301, 4.3-1050, 2.1-275 and 3.0-13.6 for algae, duckweed, snails, catfish and crayfish soft tissue, respectively. Estimates of bioconcentration ratios based on levels of arsenic in tissues and water samples in the second study were much lower than those estimated from ^{14}C, but comparable with those estimated in the first study. The investigators speculated that the ^{14}C of cacodylic acid was incorporated into a variety of degradation products.

Stary et al. (1982) assessed the accumulation of cacodylic acid by guppies, Poecilia reticulata, from both water and food. Fish kept in solutions of radiolabeled ^{74}As-cacodylic acid (10^{-5} mol/ℓ) for several days showed only negligible levels of radioactivity. ^{74}As-cacodylic

acid-contaminated fish food was given to fish for 1-2 hours before fish were washed with distilled water and transferred to clean containers and fed uncontaminated food for the duration of the study (Stary et al., 1980). Radiolabeled cacodylic acid consumed by fish through the diet was lost in a biphasic manner. The initial 95% of activity had a half-life of 0.3±0.1 days, with the remaining activity decreasing by 50% each 35±5 days.

The calculated BCF for cacodylic acid based on the log K_{ow} value of -1.78 (see Section 1.2.) and the regression equation, log BCF = 0.76 log K_{ow}-0.23 (Lyman et al., 1982), is estimated to be 0.03. This value does not agree with experimental BCF values of 100-1000 generated in the studies cited above, although the experimental values were based on ^{14}C levels. The calculated BCF supports the speculation that cacodylic acid degrades rapidly and should not bioaccumulate significantly in aquatic organisms. A calculated BCF based on a water solubility of 667,000 mg/ℓ for cacodylic acid (see Section 1.2.) and the regression equation, log BCF = 2.791-0.564 log S (Lyman et al., 1982) is estimated to be 0.32. This value also supports the conclusion that cacodylic acid is not likely to accumulate in tissues of aquatic organisms, although the bioaccumulation of arsenic from the in vivo degradation of cacodylic acid is possible.

4.1.3. Effects on Flora.

4.1.3.1. TOXICITY -- Oliver et al. (1966) assessed the effect of cacodylic acid on productivity of pond algae. Six 300 mℓ samples of pond water laden with algae and treated with concentrations of cacodylic acid ranging from 5.53 (equivalent to 2 lbs/acre) to 162 ppm. Productivity was assessed by the presence of chlorophyll, as determined by spectrophotometric methods. Concentrations of cacodylic acid >55.3 ppm (equivalent to 15 lbs/acre) resulted in a 50% reduction in productivity after 48 hours.

Roederer (1986) demonstrated that exposure of the freshwater golden brown alga, Poterioochromonas malhamensis, to 35 mM of the sodium salt of cacodylic acid blocked cytokinesis in these algae thereby inhibiting reproduction.

4.1.3.2. **BIOCONCENTRATION** -- Stary and Kratzer (1982) assessed the uptake of cacodylic acid by the alga, Chlorella kessleri. Accumulation was expressed by the cumulation factor F calculated from the equation $F = A_a/(A_m N_a V_a)$, where A_a = radioactivity of the algae, A_m = radioactivity of the medium, N_a = number of algal cells (cm^3) and V_a = mean geometric volume of one cell (cm^3). Experiments were conducted for 3 hours at 22°C. The investigators reported that equilibrium was achieved after 1 hour and was pH independent. The log F value for cacodylic acid was reported as ~1.25; the log F values for arsenic acid and methylarsonic acid were ~2.5 and 2, respectively.

4.1.4. **Effects on Bacteria.** Pertinent data regarding the effects of exposure of aquatic bacteria to cacodylic acid could not be located in the available literature as cited in Appendix A.

4.2. TERRESTRIAL TOXICOLOGY

4.2.1. **Effects on Fauna.** Del Rivero (1981) investigated the potential of cacodylic acid as a molluscicide for snails, Helix aspersa and Theba pisana. Baits were prepared from the commercial product Phytar 560 (29.8% active ingredient of cacodylic acid) with medium size wheat bran and water but without attractants. H. aspersa were given baits at 28°C with percentages of active ingredients of 1.5, 1.9 and 2.4. Respective mortality levels were 42.5, 32.5 and 67.5%. Experiments with T. pisana were conducted at 28°, 20° and 23°C and three levels of active ingredient, 1.5, 1.9 and 2.4%. Mortality levels in all experiments ranged from 67.5-97.5%.

4.2.2. Effects on Flora. Pertinent data regarding the effects of cacodylic acid on flora could not be located in the available literature as cited in Appendix A.

4.3. FIELD STUDIES

Oliver et al. (1966) assessed the effects of cacodylic acid on sandhill, hammock and grassland communities. Cacodylic acid was applied to plots along a survey line passing through a sandhill community at rates of 2, 6 and 30 lbs/acre. Effects on vegetation were noted after 1 month. An uneven distribution of vegetation in the hammock community required that cacodylic acid be sprayed on individual plants at rates corresponding to 2 and 30 lbs/acre. Effects on treated plants were assessed after 2 weeks. Three 1 rod square plots and 2-10 foot square plots of grassland were treated with cacodylic acid application rates of 2, 15 and 30 lbs/acre and 6 and 6 lbs/acre, respectively. Effects on grasses were assessed after 2 and 4 weeks.

The investigators reported that an application of 2 lbs/acre to the sandhill community did not result in a modification of the community, but that repeated applications of cacodylic acid at this rate would modify the plant community structure. An application of 30 lbs/acre resulted in a complete kill among sandhill flora. It did not appear likely that sandhill fauna would be affected directly by field concentrations of cacodylic acid, but that changes in the structure of the plant community would indirectly affect the faunal community. The investigators speculated that a completely denuded sandhill community would require 20-30 years to recover. Heavy rains minimized the effects of cacodylic acid on flora of the hammock community, but the investigators reported that plants treated with 30 lbs/acre exhibited brown leaves or were defoliated within 2 weeks. Application of cacodylic acid to grassland plots at concentrations of 2, 15 and 30 lbs/acre resulted in 50, 75-90 and 100% kill of grasses. Recovery

of treated plots was inversely related to the application of cacodylic acid. Recovery of 2 lbs/acre-treated plots was nearly complete, while little recovery was observed in 30 lbs/acre-treated plots 1 month after treatment.

4.4. AQUATIC RISK ASSESSMENT

Insufficient data prevented the development of a criterion for the protection of freshwater life exposed to cacodylic acid (Figure 4-1). Development of a freshwater criterion requires the results of acute assays with a salmonid fish species, a chordate other than bluegill sunfish, an insect, a non-Athropod/Chordate and a new insect or phylum representative. Results from chronic assays required for the development of a freshwater criterion include assays with two species of fauna and at least one flow-through bioconcentration study. There were no data available regarding the effects of exposure of marine fauna or flora to cacodylic acid, precluding the development of a saltwater criterion.

4.5. SUMMARY

The 96-hour LC_{50}s for mosquitofish and southern toad tadpoles were estimated to be between 100 and 1000 mg/ℓ (Oliver et al., 1966). The 96-hour LC_{50}s for bluegills, amphipods and shrimp were 17, 140 and 135 and 28 mg/ℓ, respectively (Mayer and Ellersieck, 1986). Cockell and Hilton (1988) reported that the NOEC for cacodylic acid in juvenile rainbow trout was $\geq$1497 µg As/g diet. Mortality was 42.5-97.5% in terrestrial snails given baits containing 1.5-2.4% cacodylic acid.

Uptake of cacodylic acid by organisms in laboratory aquatic ecosystems was greatest in algae, aquatic plants and daphnids, followed by snails, fish and crayfish. Bioconcentration ratios in these organisms ranged from a high of ~1650 for algae and daphnids to ~1-15 for fish and crayfish (Isensee et

Family	Test Type		
	Acute*	Chronic*	ECP*
#1 Chordate (Salmonid-fish)	NA	NA	NA
#2 Chordate (warmwater fish)	17*	NA	NA
#3 Chordate (fish or amphibian)	NA	NA	NA
#4 Crustacean (planktonic)	28*	NA	NA
#5 Crustacean (benthic)	137*	NA	NA
#6 Insectan	NA	NA	NA
#7 Non-Arthropod/-Chordate	NA	NA	NA
#8 New Insectan or phylum representative	NA	NA	NA
#9 algae	NA	NA	NA
#10 Vascular plant	NA	NA	NA

Example 1. Organization chart for listing Genus Mean Acute Values (GMAVs) required to derive numerical water quality criteria by the method of EPA/OWRS (1986) for the protection of freshwater aquatic life exposed to cacodylic acid.

*NA=Not Available *96-hour LC_{50} in mg/L for bluegill sunfish, Lepomis macrochirus *96-hour LC_{50} in mg/L for shrimp, Palaemonetes kadiakensis *96-hour LC_{50} in mg/L for the amphipod, Gammarus fasciatus.

FIGURE 4-1

Organization Chart for Listing GMAVs
Required to Derive Numerical Water Quality Criteria by the Method
of U.S. EPA/OWRS (1986) for the Protection of Freshwater Aquatic
Life Exposed to Cacodylic Acid

al., 1973; Schuth et al., 1974). Stary et al. (1982) demonstrated that uptake of cacodylic acid by guppies from water was neglible after a few days of exposure and that 95% of the tissue residues from ingested cacodylic acid was depurated within hours. Calculated BCFs estimated from log K_{ow} and water solubility were <1, suggesting that cacodylic acid was not likely to accumulate in the tissues of aquatic organisms.

Algal productivity was reduced by 50% in the presence of 55.3 ppm cacodylic acid for 48 hours (Oliver et al., 1966). Reproduction in brown algae was inhibited by 35 mM of the sodium salt of cacodylic acid (Roederer, 1986).

Field studies revealed low to moderate effects on vegetation from three terrestrial communities exposed to 2 lbs/acre of cacodylic acid. Treatment levels of 30 lbs/acre were highly detrimental to the survival of vegetation in those communities (Oliver et al., 1966).

5. PHARMACOKINETICS

5.1. ABSORPTION

Stevens et al. (1977) compared the absorption of cacodylic acid following intravenous, intratracheal and oral administration of the compound. Intravenous absorption was assumed to represent 100%. Lung absorption was determined by administering a single 78 mg/kg dose of ^{14}C-labeled cacodylic acid in 100 µl of aqueous solution to young adult male Sherman strain rats intratracheally by a cannula inserted between the 4th and 5th tracheal rings. Following dosing, lungs and trachea were excised at 0, 5, 10 and 20 minutes and assayed for ^{14}C-cacodylic acid equivalent. The amount absorbed was estimated as the difference between the amount administered and the amount remaining in the excised organs. Results showed that lung absorption was rapid and almost complete; 5% remained in the lung 15 minutes posttreatment, and the half-time for absorption was estimated at 2.2 minutes. The plasma ^{14}C-concentration vs. time curve resulting from intratracheal administration of 33 µg ^{14}C-cacodylic acid was similar to that generated following intravenous injection, with maximal concentration observed at 5 and 10 minutes, providing further evidence of the rapid absorption rate characteristic of this route. These data were derived from sequential samples of blood collected from the interorbital sinus (number of animals used was not reported). Percent absorption from the lungs 24 hours after an intratracheal dose of 33 µg ^{14}C- and 13.8 µg ^{74}As-labeled cacodylic acid was 92%, which was determined by combining amounts retained in body tissues (~24% of dose), excreted in urine (~60%), and in feces (~8%). In a separate part of this study, cumulative $^{14}CO_2$ expiration was measured over 24 hours following a single intratracheal dose of ^{14}C-cacodylic acid. Expired $^{14}CO_2$ accounted for only 0.0069% of the

dose, indicating that failure to recover and measure $^{14}CO_2$ in the estimation of lung absorption described above had no discernible effect on the result.

In another part of the same study using male Sherman rats, GI absorption of a single 0.5 mℓ gavage dose of 33 µg ^{14}C- and 6.9 µg ^{74}As-cacodylic acid dissolved in water was estimated by sacrificing the rats at 4 hours posttreatment and assaying the digestive tract for equivalent percent of administered dose remaining. A GI absorption half-time of 248 minutes was estimated. Plasma levels following absorption from the GI tract peaked at ~1 hour. From other similarly treated rats the investigators estimated that 66% of the dose was absorbed at 24 hours, with ~32% retained in body tissues and ~25% excreted in urine. About 31% was eliminated in the feces, of which only a minute fraction appears be of biliary origin (biliary secretion at 2 hours was 0.226% of dose). Since the amount of cacodylic acid eliminated by the lungs as $^{14}CO_2$ was very minor (equivalent to 0.13% of a 200 mg/kg oral dose of ^{14}C-cacodylic acid in 24 hours), it had little effect upon absorption estimations.

Excretion data on hamsters and mice support the estimates of GI absorption determined in rats. Yamauchi and Yamamura (1984) administered cacodylic acid at 40 or 50 mg/kg by gavage to male Syrian golden hamsters and measured total arsenic excretion in urine and feces over a 5-day collection period. When corrected for pretreatment values, total urinary excretion accounted for 48.9% of the dose, with 92% of that recovered within the first 24 hours. Fecal excretion accounted for 36% of the dose. Marafante et al. (1987) administered ^{74}As-cacodylic acid by gavage to male NMRI mice and male hamsters at 40 mg As/kg and measured radioactivity in urine and feces over a 48-hour collection period. From hamsters, 41.2% of the dose of

radioactivity was recovered from the feces and 56.3% from the urine (total recovery = 97.5%), while 29.2% was recovered from the feces and 67.6% from the urine in mice (total recovery = 96.8%).

In one male volunteer given a single oral dose of cacodylic acid of 0.1 mg As/kg, urinary excretion of cacodylic acid and a metabolite accounted for ~84% of the dose in 3 days (Marafante et al., 1987). These data suggest that cacodylic acid is well absorbed by the human GI tract. Urinary excretion of 75% of the arsenic of an oral dose (500 μg As) of sodium dimethylarsinate in 4 days in four volunteers (Buchet et al., 1981) is further support for a GI absorption factor for humans of at least 80%.

Hwang and Schanker (1973) studied the in vivo rate and mechanism of intestinal absorption of cacodylic acid in Charles River-derived male rats. One mℓ of a 5 mM solution of cacodylic acid in modified Krebs-Ringer phosphate solution (pH 6.7) was injected into the intestinal lumen following surgical placement of ligatures that blocked conduction by the lumen, but did not occlude major blood vessels. Intestinal cacodylic acid content was assayed over a 4- to 5-hour absorption period. Absorption data over this time fit a first-order process, with a rate constant of 0.207 $hour^{-1}$ and a half-time of 201 minutes, a value not appreciably different from that in the Stevens et al. (1977) study discussed previously.

The mechanism of absorption was determined by Hwang and Schanker (1973) to be by a nonsaturable transfer process, probably passive diffusion. Increasing the concentration of administered compound by 100-fold did not yield evidence of saturation. By comparing absorption rate coefficients with molecular weights of two other organic arsenicals, it was shown that molecular size does not influence absorption rate, thereby indicating that movement by aqueous channels (membrane pores) was an unlikely pathway.

5.2. DISTRIBUTION

Stevens et al. (1977) studied the tissue distribution following both high and low doses of cacodylic acid. High-dose distribution of radioactivity was studied in young adult male Sherman rats sacrificed at 0.117, 0.25, 1, 24, 72 and 168 hours after intravenous dosing with ^{14}C-cacodylic acid in aqueous solution at 200 mg/kg (0.5 mℓ/150 g bw). Blood, lung, liver, brain, spleen and kidney concentrations, in terms of the ^{14}C-cacodylic acid-equivalent, were measured and reported as a percent of the dose recovered. Additional rats were dosed similarly, and whole blood was collected at selected intervals from the intraorbital sinus and assayed for blood clearance by separating plasma and erythrocytes, then counting the radioactivity of each. The plasma concentration vs. time plot showed triphasic elimination with half-times of 0.014 and 3.42 hours, and permitted estimation of an apparent volume of distribution of 15.3 mℓ. At 15 minutes, the highest tissue concentrations from this high-dose intravenous test were in whole blood (12.5%) and liver (9.81%), followed by kidney (2.98%), lung (0.61%), spleen (0.20%) and brain (0.08%). Concentrations were reduced in all tissues except blood (14.8%) at $\geq$1 hour postdosing.

Low-dose distribution in adult male Sherman rats was measured by giving a fixed volume of 0.5 aqueous solution containing 33 μg of ^{14}C-cacodylic acid and a varied amount ranging from 3.47-13.99 μg ^{74}As-cacodylic acid (adjustment of amount was required because of its short half-life). The dose was given intravenously, intratracheally or orally. A comparison of whole blood radioactivity concentration-time curves revealed higher concentrations ~8 hours after oral dosing than by the other two routes. Whole body retention at 24 hours was slightly greater after oral administration

(31.8% dose) than after intratracheal (24.3%) or intravenous (20.5%) administration. Contrast between whole blood and plasma levels showed that cacodylic acid was cleared rapidly from the plasma, but became bound to erythrocytes. The investigators suggested that the rat RBC has a high affinity for cacodylic acid, but that there is considerable intraspecies variation with regard to the affinity of the RBC for cacodylic acid. Half-times for whole blood clearance were 90 days after intravenous, 76 days following intratracheal and 90 days after oral dosing.

No significant differences in the percent dose recovered from tissues were found following intravenous administration of high- and low-dose levels, except for proportionally lower levels in the liver and higher levels in the kidney 15 minutes after dosing at the lower dosage level. This indicates little or no dose dependency on tissue distribution of cacodylic acid over the dose range tested. Table 5-1 shows comparative low-dose tissue levels for the three routes at 105 days posttreatment. Residues, although slight in some cases, remain in all tissues. Significant route-dependent differences in tissue levels noted at this time were few: tissue levels in the spleen and kidney were higher after intratracheal administration than after intravenous administration, and oral dosing led to higher levels in the liver than did intravenous injection.

Pregnant CD rats were treated with a single 33 µg dose of ^{14}C-cacodylic acid to study placental transfer (Stevens et al., 1977). Levels of radioactivity were measured at 24 hours after treatment on day 21 of gestation in maternal and fetal whole blood, brain, kidney and liver. The results indicated that cacodylic acid crosses the placenta readily and distributes to fetal tissues at concentrations similar to those of the dam. Exceptions to this were the brain (lower levels) and kidney (higher levels) in the fetus ($p>0.05$).

TABLE 5-1

Tissue Distribution of ^{14}C 105 Days After Administration of ^{14}C-Cacodylic Acid to Adult Male Sherman Rats by Various Routes[a,b]

Tissue	ng/g Fresh Tissue		
	Intravenous	Intratracheal	Oral
Heart	4.86 ± 1.55 (0.02)[c]	7.39 ± 1.70 (0.02)	8.47 ± 1.33 (0.05)
Lung	16.8 ± 1.22 (0.09)	20.2 ± 5.40 (0.07)	24.8 ± 5.93 (0.11)
Spleen	15.8 ± 2.87 (0.03)	41.2 ± 7.81[d] (0.07)	31.5 ± 7.87 (0.06)
Liver	5.86 ± 0.66 (0.19)	5.58 ± 2.56 (0.29)	15.7 ± 5.69 (0.54)
Kidney	5.75 ± 0.33 (0.04)	13.9 ± 2.70[d] (0.08)	9.68 ± 1.82 (0.07)
Brain	1.66 ± 0.22 (0.01)	2.84 ± 1.28 (0.01)	1.82 ± 0.48 (0.01)
Testes	1.22 ± 0.22 (0.02)	1.28 ± 0.14 (0.01)	1.69 ± 0.12 (0.02)
Muscle	0.88 ± 0.22 (0.47)	0.85 ± 0.28 (0.33)	0.85 ± 0.36 (0.45)

[a]Source: Stevens et al., 1977

[b]All rats were given a single 33 µg dose of ^{14}C-cacodylic acid by either of three routes in addition to 3.5 µg intravenously, 13.8 µg intratracheally and 6.9 µg orally of ^{74}As-cacodylic acid.

[c]Mean percent of total dose per tissue in parentheses (n=4).

[d]Difference from intravenous dose at $p<0.05$.

Yamauchi and Yamamura (1984) administered a single oral (gavage) dose of 50 mg/kg cacodylic acid to male Syrian golden hamsters (Section 5.3.), and measured levels in blood, brain, hair, kidney, liver, lung, muscle, skin and spleen at several time points up to 120 hours after treatment. The compound was found in all tissues, reaching a peak in concentration 6 hours post-treatment in all tissues except hair. Highest levels at 1 hour were found in lung > spleen > kidney > liver > skin > muscle ~ brain. Concentrations of cacodylic acid decreased to amounts equivalent to controls within 72 hours posttreatment in all tissues except the hair and lung. This differs somewhat from findings in the rat (Stevens et al., 1977), suggesting to the authors of the current study that in vivo retention varies between species.

5.3. METABOLISM

Yamauchi and Yamamura (1984) studied the metabolism of cacodylic acid in male Syrian golden hamsters. A single gavage dose of 40 or 50 mg/kg bw (vehicle unspecified) was administered by stomach tube, and the metabolites were measured in tissues and excrement. Methylarsonic acid values slightly above pretreatment levels were observed in the brain, kidneys, lung and urine. Inorganic arsenic was slightly, but significantly, increased over control values in the blood, kidneys and lungs. Also, the excreted amounts of inorganic arsenic in urine and feces were 11.9 µg greater than the sum of pretreatment values plus inorganic arsenic present as a contaminant in the test sample of cacodylic acid. This suggested the possibility that a small amount of in vivo demethylation occurs in hamsters.

Marked elevations in the levels of a form of TMA compound were found in the liver, kidneys, lungs, muscle and brain, from 1 hour posttreatment (24

hours in urine, which was the first sample time for this body fluid) to the end of the observation period, 120 hours. TMA concentration was highest in the liver. These observations suggest that substantial methylation of cacodylic acid occurs in vivo in the hamster, and that the liver is the site of this metabolic pathway. The TMA biosynthesized by hamsters was believed to be in a form such as arsenobetaine rather than as the highly toxic TMA, but the exact chemical structure of this TMA-like product has not yet been elucidated.

In the Stevens et al. (1977) rat study with ^{14}C- and ^{74}As-labeled cacodylic acid (see Section 5.2.), no differences were reported in the tissue distribution of the ^{74}As- and ^{14}C-labels. The authors concluded that substantial conversion in vivo from organic to inorganic arsenic did not appear to occur in the rat; however, they did not rule out the possibility of valence state changes. The recovery of only minor amounts ($\leq$0.13% of dose) of ^{14}C-cacodylic acid as expired $^{14}CO_2$ is further evidence that demethylation to inorganic arsenic is a minor pathway (Stevens et al., 1977). Marafante et al. (1987) did not detect any inorganic arsenic in the excrement of mice or hamsters treated orally with ^{74}As-cacodylic acid (40 mg As/kg bw), or in the urine of a male volunteer who ingested cacodylic acid corresponding to 0.1 mg As/kg bw. No additional metabolic breakdown products were found by Marafante et al. (1987). Oral administration of cacodylic acid to mice, hamsters and a human resulted in the excretion of unmetabolized cacodylic acid, cacodylic acid complex and TMAO in the urine and feces (Tables 5-2 and 5-3). These results are at variance with the generally accepted assumption that cacodylic acid is the endpoint in the detoxification of inorganic arsenics. Marafante et al. (1987) suggested

TABLE 5-2

Excretion of Metabolites of Cacodylic Acid in the Urine Following Oral Administration[a]

Species	% of Dose		
	Cacodylic Acid	Cacodylic Acid Complex	TMAO
Hamster[b]	38.7	11.2	6.4
Mouse[b]	56.4	7.7	3.5
Human[c]	80	NR	3.6

[a]Source: Marafante et al., 1987

[b]Single dose of ^{74}As-cacodylic acid by gavage at 40 mg As/kg; excreta collected for 48 hours; n=5.

[c]Single dose of ^{74}As-cacodylic acid at 0.1 mg As/kg; urine collected for 3 days

NR = Not reported; TMAO = trimethyl arsine oxide

TABLE 5-3

Excretion of Metabolites of Cacodylic Acid in the Feces Following Oral Administration[a]

Species	% of Dose		
	Cacodylic Acid	Cacodylic Acid Complex	TMAO
Hamster[b]	37.3	3.9	ND
Mouse[b]	24.3	4.9	ND
Human	NR	NR	NR

[a]Source: Marafante et al., 1987

[b]Single dose of ^{74}As-cacodylic acid by gavage at 40 mg As/kg; excreta collected for 48 hours; n=5.

ND = Not detected; NR = not reported; TMAO = trimethyl arsine oxide

that cacodylic acid may react with SH-containing compounds such as 2-mercaptoethanol, cysteine, glutathione and lipoic acid in a reducing step, which is followed by oxidative methylation by S-adenosylmethionine to form TMAO. Thus, the cacodylic acid complex is believed to be an intermediary step in the further methylation to TMAO, probably occurring in the liver.

5.4. EXCRETION

Elimination of cacodylic acid is believed to be faster than that of inorganic arsenic (Vahter, 1983). Inorganic arsenic is methylated in the body, a detoxification process that renders the arsenic less reactive and facilitates its excretion by the kidney.

Stevens et al. (1977) found the rate of excretion of cacodylic acid to be very rapid in rats. With peroral dosing (33 µg ^{14}C-cacodylic acid), the primary route of excretion was fecal (31% of the dose) with 25% in urine. Urinary excretion after intratracheal and intravenous treatment at a similar dosage was $\geq$60%. The minor amounts excreted in feces after intravenous treatment (1.18% of the dose) are believed to be a result of biliary secretion. Minor amounts of radiolabel were eliminated as CO_2, <0.01% of the dose 24 hours following intravenous or intratracheal administration and ~10-fold higher after oral administration.

Yamauchi and Yamamura (1984), in their study with the golden hamster, found that 24 hours after administration of 40 mg/kg bw of cacodylic acid by gavage, 45% was excreted in urine and 34.7% in feces. At 5 days posttreatment, 84.9% of the total dose administered was excreted in urine and feces, suggesting that some accumulation may occur in hamsters. No data regarding excretion by lungs were reported.

Excretion of cacodylic acid in mice, hamsters and humans was studied by Marafante et al. (1987) (see Tables 5-2 and 5-3). More than 96% of the dose

was excreted by mice and hamsters after 2 days. Fecal excretion was 41.2%, in the hamster and 29.2% in the mouse. Urinary excretion in the hamster was 56.3%, and in the mouse, 67.6%. In the human study, ~84% of the dose 3 days postingestion was excreted in urine. Buchet et al. (1981) recovered 75% of the arsenic from an oral dose of sodium dimethylarsinate (500 mg As) in the urine of four male volunteers in 4 days.

5.5. SUMMARY

Cacodylic acid appears to be asorbed rapidly and virtually completely from the respiratory tract of intratracheally treated rats, with a half-time of 2.2 minutes (Stevens et al., 1977). Gastrointestinal absorption in rats is considerably slower, with an estimated half-time of 248 minutes (Stevens et al., 1977). Excretion data in rats (Stevens et al., 1977), hamsters (Yamauchi and Yamamura, 1984; Marafante et al., 1987) and mice (Marafante et al., 1987) indicate that GI absorption ranges from ~60-70% in these species. Urinary excretion data in humans (Marafante et al., 1987; Buchet et al., 1981) suggest a GI absorption factor for humans of ~80%.

Distribution data obtained from rats treated intravenously with high (200 mg/kg) and low (33 µg) doses indicate that the rat RBC has an affinity for cacodylic acid (Stevens et al., 1977). Among other tissues, highest concentrations were found in the liver > kidney > lung > spleen > brain. The magnitude of the dose had no effect on tissue distribution. Plasma elimination was triphasic, with a terminal half-life of 3.42 hours. Tissue distribution appeared to be similar in hamsters, except that the hamster RBC did not appear to have a particular affinity for cacodylic acid (Yamauchi and Yamamura, 1984).

The metabolism of cacodylic acid has been studied by quantifying its metabolites in tissue, expired air and excreta of treated rats, mice, hamsters and humans (Stevens et al., 1977; Yamauchi and Yamamura, 1984;

Marafante et al., 1987). Excretion data in hamsters, mice and humans suggest that metabolism is not nearly as important as excretion in the elimination of cacodylic acid (Marafante et al., 1987). Demethylation to methylarsonic acid, inorganic arsenic and carbon dioxide appears to be a minor metabolic pathway (Yamauchi and Yamamura, 1984; Stevens et al., 1977). The most important biotransformation pathway appears to be methylation to a trimethyl compound, probably to a trimethylarsine oxide conjugate (Yamauchi and Yamamura, 1984; Marafante et al., 1987). Complexation with thio-containing compounds may be an intermediate step in the formation of trimethylarsine oxide.

Excretion of a parenteral dose is primarily through the kidney, with minor amounts expired as CO_2 and excreted through the bile (Stevens et al., 1977; Marafante et al., 1987). Fecal excretion of an oral dose probably represents largely unabsorbed compound. A plasma half-life in rats of 3.42 hours was estimated for the terminal phase of a triphasic decay function (Stevens et al., 1977). In hamsters and mice, urinary and fecal excretion together accounted for 97.5 and 96.8% of an oral dose after 48 hours, suggesting that excretion in these species is fairly rapid (Marafante et al., 1977). In humans, ~80% of an oral dose was recovered from the urine within 3 days of treatment (Marafante et al., 1987; Buchet et al., 1981).

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposures. Pertinent data regarding inhalation exposure to cacodylic acid could not be located in the available literature as cited in Appendix A.

6.1.2. Oral Exposures.

6.1.2.1. SUBCHRONIC -- In a study by Nees (1968) with weanling Sprague-Dawley rats, dietary levels of 0, 3, 15, 30 and 100 ppm cacodylic acid were administered for 30-90 days. Data in the CBI files indicated that these dietary levels actually represented arsenic, and the equivalent corresponding dietary concentrations of cacodylic acid were calculated as 0, 5.5, 27.6, 55.3 and 184 ppm, respectively. Because the original study was not available, exact details were lacking. Urinalysis, hematological studies and gross pathology examinations were performed. No significant effects on body weight, food consumption, hematology, organ weight or histology could be attributed to the test substance. It is not clear if the testis was among the organs examined.

In a 20-day study by Nees (1960), weanling Sprague-Dawley rats were fed diets that provided cacodylic acid at dosages of 0, 70, 140 or 280 mg/kg. At a dose of 280 mg/kg, histological examination showed reduced activity of spermatogonia cells, along with atrophic changes in seminiferous tubules, but no adverse effects were noted in the cerebrum, cerebellum, heart, lungs, liver, spleen, kidney, pancreas, adrenals, stomach intestines, urinary bladder or bone. A NOAEL of 140 mg/kg was reported.

Derse (1968) conducted a 90-day feeding study using 32 beagle puppies. Three groups of four males and four females each received dietary levels of cacodylic acid of 0, 3, 15 or 30 ppm. Body weights were recorded weekly.

At 90 days, endpoints examined were kidney and liver function, urinalysis and histopathology of major organs and tissues. No significant differences were found between test groups and controls, and no mortality was noted in any test group. Lesions in the brain, heart, liver, kidney, spleen, intestine and other organs occurred randomly among both experimental and control groups and were therefore not attributed to cacodylic acid. It is unclear whether the testis was examined histologically.

The Weed Science Society of America (1983) reported briefly on a study obtained from Vineland and Crystal Chemical Company. Groups of 10 rats (strain not reported) were fed doses of 226, 118, 54 or 0 mg/kg for 3 weeks. A LOAEL was determined at 226 mg/kg, associated with atrophic changes in seminiferous tubules and decreased activity of spermatogonia cells. The 118 mg/kg group did not differ from the controls; therefore, 118 mg/kg represents a NOAEL. No other details of this study were given.

6.1.2.2. CHRONIC -- Pertinent data regarding chronic oral exposure to cacodylic acid could not be located in the available literature as cited in Appendix A. The Office of Pesticide Programs (OPP, 1987) reports that chronic data are being generated.

6.1.3. Other Relevant Information. Data regarding the acute toxicity of cacodylic acid are presented in Table 6-1. Oral LD_{50} values for rats ranged from 644-1433 mg/kg. No marked age or gender related effects on the acute toxicity of cacodylic acid were apparent in rats. Data for rats and mice are similar for the inhalation and intraperitoneal routes of exposure.

No information regarding toxicity of cacodylic acid to humans by oral or inhalation routes was found; however, workers using arsenic-containing silvicides for tree-thinning purposes had higher urinary concentrations of

TABLE 6-1

Acute Lethal Toxicity of Cacodylic Acid

Species	Sex	Route	LD_{50} or 2-Hour LC_{50}	Reference
Rats	adult males	oral	1315 mg/kg	Gaines and Linder, 1986
Rats	adult females	oral	644 mg/kg	Gaines and Linder, 1986
Rats	weanlings, both sexes	oral	1433 mg/kg	Gaines and Linder, 1986
Rats	NR	oral	700 mg/kg	Farm Chemicals Handbook, 1987
Rats	both sexes	oral	830 mg/kg	Weed Science Society of America, 1983
Rats	NR	oral	1350 mg/kg	Bailey and White, 1965
Rats	males	oral	700 mg/kg	Nees, 1960
Rats	males	inhalation	6.9 mg/ℓ	Stevens et al., 1979
Rats	females	inhalation	3.9 mg/ℓ	Stevens et al., 1979
Mice	both sexes	inhalation	6.4 mg/ℓ	Stevens et al., 1979
Rats	females	intravenous	470 mg/kg	Stevens et al., 1979
Rats	males	intraperitoneal	720 mg/kg	Stevens et al., 1979
Rats	females	intraperitoneal	520 mg/kg	Stevens et al., 1979
Mice	males	intraperitoneal	520 mg/kg	Stevens et al., 1979
Mice	females	intraperitoneal	600 mg/kg	Stevens et al., 1979
Mice	adult males	intraperitoneal	500-1000 mg/kg	Pizak et al., 1963
Mice	NR	NR	185 mg/kg	Mel'nikov, 1971

arsenic compounds (>0.3 mg/ℓ), including cacodylic acid, than did the unexposed control group (0.03-0.14 mg/ℓ) (Tarrant and Allard, 1972). Concentrations in workers were generally near normal on Monday and high on Friday. No evidence of arsenic poisoning was observed, and urinary levels did not appear to increase over time. Personnel took protective measures, including use of protective clothing and skin creams, and thorough post-exposure washing.

In another study (Wagner and Weswig, 1974) that tested urinary excretion and blood levels of arsenic in five workers exposed to cacodylic acid for 2 months, urinary arsenic correlated more closely with exposure levels than did blood levels, and there was an immediate increase in the daily excretion rates. Levels dropped back to normal when exposure was discontinued. Workers reported a strong odor of garlic in the work area. Arsine gas is characterized by such an odor, suggesting that perhaps the cacodylic acid was being converted to this toxic gas.

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the inhalation carcinogenicity of cacodylic acid could not be located in the available literature as cited in Appendix A.

6.2.2. Oral. Oral cancer studies were limited to one long-term carcinogenicity study by BRL (1968) and Innes et al. (1969). In the study, two strains of mice were tested [(C57BL/6 x C3H/Anf)F1 (B6C3F1) and (C57BL6 x AKR)F1 (B6AKF1)]. Dose levels chosen were maximum tolerance levels. Groups of 18 males and 18 females of each strain were administered 46.4 mg/kg bw/day in distilled water by gavage from 7-28 days of age. On day 28, adjustments were made for body weight changes, and a concentration (121 ppm)

calculated to deliver an equivalent daily dose was added to the diet for the remainder of the 80-week test period. Eleven male and 18 female BC6C3F1 mice and 17 male and 16 female B6AKF1 lived until the end of the test. Although pulmonary adenoma, uterine leiomyoma and incidental lesions occurred in a few animals, the incidence was not significantly different from that of untreated and pooled controls.

Cacodylic acid has not been scheduled for carcinogenicity testing by the NTP (1988).

6.2.3. Other Relevant Information. In another BRL (1968) study, which used the same strains of mice reported above, a single subcutaneous injection of cacodylic acid at 464 mg/kg bw in distilled water was administered in the nape of the neck to 28-day weanlings to screen for "strong" carcinogenicity. Results were negative, with tumor incidences not significantly increased over controls.

Johansen et al. (1984) studied the promoting effect of cacodylic acid on tumors induced in male Wistar rats by DENA. Partially hepatectomized rats were injected intraperitoneally with saline (controls) or 30 mg/kg of DENA. On postsurgery day 7, 80 ppm (MTD) cacodylic acid was administered in drinking water to both groups. The investigators estimated an average dose of ~3.8 mg/rat/day. Body weight was monitored weekly, and rats were sacrificed and necropsied after 6 months. Histopathological examinations were limited to the liver and kidney. Renal tumors developed in 2/11 DENA control rats and 3/7 rats receiving both compounds (statistically insignificant); cacodylic acid treatment alone produced no tumors (0/8). A nonsignificant increase in liver lesions, basophilic foci and neoplastic nodules occurred among rats receiving DENA and cacodylic acid, but not among the controls.

The authors concluded that these results suggest a tumor promoting effect of cacodylic acid despite the lack of statistical significance, which might be shown if an increased number of animals had been studied and if the dose of DENA had been reduced.

6.3. MUTAGENICITY

Cacodylic acid has been tested for mutagenicity and genotoxicity in bacteria, yeast, Drosophila and mammalian cell cultures with mixed results (Table 6-2). Consistently positive test results were obtained in Saccharomyces cerevisiae (Simmon et al., 1977; Jones et al., 1984; Riccio et al., 1981).

Differential toxicity tests with Escherichia coli were reported to be negative by Simmon et al. (1977); however, Jones et al. (1984) re-examined data from Simmon et al. (1977) and suggested that their test should be regarded as inconclusive (reason not given). A reverse mutation test also conducted by Simmon et al. (1977) and using E. coli appears to be unequivocally negative. Tests in Salmonella typhimurium were consistently negative (Simmon et al., 1977; Andersen et al., 1972).

Tests using Drosophila also produced negative or equivocal results. The nondisjunction test was clearly negative (Ramel and Magnusson, 1979). Although the sex-linked recessive lethal test (Valencia, 1981) was judged to be negative, there were some problems with maintaining replicates in both experimentals and controls, which was considered to weaken this data point.

Results from mammalian cell tests were mixed. The co-mutagenicity (Taylor et al., 1984) and sister chromatid exchange (Jones et al., 1984) tests using Chinese hamster ovary cells were negative, as was the unscheduled DNA repair synthesis test (Simmon et al., 1977). Both the forward mutation test and micronucleus test (Jones et al., 1984) showed positive mouse tissue sensitivity to cacodylic acid as a mutagen.

TABLE 6-2

Mutagenicity Testing of Cacodylic Acid

Assay	Indicator Organism	Purity (%)	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Microbiological Assays								
Reverse mutation	Escherichia coli WP2 (UvrA-)	65.6	plate incorporation	NR	-/+	-/-	NC	Simmon et al., 1977
Reverse mutation	Salmonella typhimurium TA1535, TA1537, TA1538, TA100	65.6	plate incorporation	NR	-/+	-/-	NC	Simmon et al., 1977
Reverse mutation	S. typhimurium TA98, TA100	technical grade	plate incorporation	500-5000 µl/plate	-/+	-/-	NC	Jones et al., 1984
Reverse mutation	S. typhimurium strain, NR	90-99	plate incorporation	1-5 µl/plate	NR	Neg.	NC	Andersen et al.,1972
Relative toxicity (DNA repair)	Bacillus subtilus H17, M45; E. coli W311D, P3478	65.6	inoculated disc, plated	1 mg/disc/plate		-/+	-/- Jones et al. (1984) reexamined results; regarded results as inconclusive	Simmon et al., 1977
Relative toxicity (DNA repair)	S. typhimurium SL4525, SL4700, TA1978, TA1538	technical grade	inoculated disc, plated	1-5 mg/disc/plate	-/+	-/-	NC	Jones et al., 1984
Mitotic recombination	Saccharomyces cerevisiae D3	65.6	suspension/plate	5%	-/+	+/+	NC	Simmon et al., 1977
Mitotic recombination	S. cerevisiae D3	technical grade	suspension/plate	1-4%	-/+	+/+	NC	Jones et al., 1984
Mitotic crossing over, gene conversion, reverse mutation	S. cerevisiae D7	technical grade	suspension/plate	0.5%	-/+	+/+	positive for all three endpoints	Jones et al., 1984
Sister chromatid exchange	Chinese hamster ovary	technical grade	cell culture	4.9 to >3000 µg/ml	-/+	-/-	NC	Jones et al., 1984

TABLE 6-2 (cont.)

Assay	Indicator Organism	Purity (%)	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Microbiological Assays (cont.)								
Forward mutation	mouse lymphoma L5178Y TK$^{-/+}$	technical grade	cell culture	<150 µg/mL 900-1000 µg/mL	-S-9 -S-9	- +	metabolic activating system appeared to press cytotoxicity and enhance mutagenic response	Jones et al., 1984
Unscheduled DNA synthesis	human fetal lung fibroblasts (WI-38 cells)	65.6	flask culture	10^{-7} to 10^{-3} log concentration	-/+	-/-	NC	Simmon et al., 1977
Reverse mutation (co-mutagenicity)	Chinese hamster ovary	NR	+GAT medium/ plated	12 µ/m	NR	-	NC	Taylor et al., 1984
Cytotoxicity LD_{50}	Chinese hamster ovary	NR	+GAT medium/ plated	1.6 mM	NR	+	LD_{Lo} NR	Taylor et al., 1984
In Vivo Assays								
Micronucleus test	mouse	technical grade	gavage or intraperitoneal injection	188+375 mg/kg bw (at onset)+ (adm. at 24 hours)	NA	negative at 48 hours positive at 72 hours, equivocal at 96 hours	low-dose group	Jones et al., 1984
				375+750 mg/kg/bw	NA	negative at 48 hours; positive at 72 hours, equivocal at 96 hours	middle-dose group	Jones et al., 1984
				750+1500 mg/kg/ bw	NA	positive at 48 hours; high mortality at 96 hours	high-dose group	Jones et al., 1984
Nondisjunction loss of sex chromosomes	Drosophila melanogaster ($YW^{3}f/yw^{3}f/y^{+}YB^{5}$)	NR	oral feeding	NR	NR	negative	NC	Ramel and Magnusson, 1979

Assay	Indicator Organism	Purity (%)	Application	Concentration or Dose	Activating System	Response	Comment	Reference
In Vivo Assays (cont.)								
Sex-linked recessive lethal	D. melanogaster males only, Canton-S wild-type stock	technical grade	oral in 1% glucose solution	3-1000 ppm	NR	negative	considered questionable because of reduced numbers of replicates; responses: 0.121% treated/ 0.047% controls	Valencia, 1981

NR = Not reported; NC = no comment; NA = not applicable

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It is clear that cacodylic acid is mutagenic in certain systems and under certain conditions. In an analysis of mutagenesis methodology for pesticides, Waters et al. (1981) classified cacodylic acid as having medium priority status for further evaluation as a mutagen or carcinogen. Using a computerized data management system, Garrett et al. (1986) analyzed the qualitative results of the work by Waters et al. (1981). Their comparison showed that, although cacodylic acid yielded positive results in eukaryotic systems (gene mutation, DNA damage and chromosomal effects), evidence for its mutagenicity is weak when compared with other pesticides.

6.4. TERATOGENICITY

Rogers et al. (1981) administered cacodylic acid (99% pure) in distilled water by gastric intubation to time-pregnant random-bred albino CD rats and CD-1 mice on days 7-16 of gestation. Day 1 was defined by demonstration of a sperm plug in mice, and presence of sperm in the vaginal smear of rats. Dams were sacrificed on day 21, and fetuses were weighed, fixed and examined for visceral and skeletal effects. For data analysis the litter was used as the experimental unit. In the rat study, between 21 and 40 rats/group were given 0 (distilled water), 7.5, 15, 30, 40, 50 or 60 mg/kg/day doses in 0.2 mℓ/day intubation volumes. Both maternal (significantly reduced body weight gain) and fetal toxicity (reduced body weight and retarded sternal and caudal ossification) were significant at 40 mg/kg/day. Maternal mortality (67%) occurred at the highest dose tested, and fetal mortality was significantly elevated at 50 mg/kg/day. Irregular palatine rugae (ridges that were discontinuous and/or not lying in apposition at the palatal raphe) occurred in a dose-related manner and were significantly different from controls at $\geq$30 mg/kg/day. No significant effect was observed at 15 mg/kg/day.

In the same study, 30-32 mice/group were administered 0, 200, 400 or 600 mg/kg/day in 0.1 mℓ/day intubation volumes. Maternal toxicity as evidenced by reduced body weight gain was significant at 200 mg/kg/day. Doses ≥200 mg/kg/day caused significant decreases in fetal weight and retardation of caudal ossification. Cleft palates resulted from doses of 400 (in 57% of litters) and 600 mg/kg/day (in 70% of litters). Fetal mortality was significantly higher at 600 mg/kg/day.

Kavlock et al. (1985) treated random-bred CD-1 mice by intubation (0.5 mℓ/mouse) on day 8 of gestation with doses of cacodylic acid (99.5% purity) expected to induce a low degree of maternal lethality (20 mice/1600 mg/kg each) or a moderate dose for maternal lethality (40 mice/2400 mg/kg each). Twenty controls received only the distilled water vehicle. On day 18 of gestation, dams were sacrificed and examined for weight gain, while fetuses were examined to determine presence of malformations and rate of development. The litter was considered the experimental unit. Maternal toxicity occurred at 1600 mg/kg (26% maternal death; reduced weight gain). A significantly high percentage of prenatal mortality occurred at 1600 mg/kg, along with reduced fetal weight. At 1600 mg/kg, delays in sternal and caudal ossification and major delays in renal papilla development occurred. The incidence of supernumerary ribs and other skeletal and soft tissue abnormalities was markedly elevated over controls at both dosages.

In a prior screening study, Chernoff and Kavlock (1982) administered a minimum toxic dose of 0 or 600 mg/kg of cacodylic acid (purity not reported) by gavage in water on days 8-12 gestation to 24 CD-1 mouse dams to assess effects on offspring. Parameters of toxicity evaluated included maternal survival and weight change and offspring survival and body weight at post-partum days 1 and 3. Increased maternal death (7/24) reduced the sample

size such that relatively large litter size reductions were not significantly different from controls; however, significantly reduced maternal and fetal weights resulted. This test was later repeated with 40 vehicle control and 30 treated mice treated at doses of 0 and 600 mg/kg of cacodylic acid as previously described (Kavlock et al., 1987). Treatment resulted in the death of four dams and a significant reduction in maternal body weight gain. Reduced fetal body weights were observed on postpartum day 3.

Outbred Lak:LVG (SYR) strain Golden hamsters were mated, and $\geq$10 pregnant females per group were injected intraperitoneally with a single dose of 900 or 1000 mg/kg sodium cacodylate (purity not reported) (judged by a pilot study to be in the range of the minimum lethal dose for pregnant females) in deionized distilled water (Hood et al., 1982). Treatments were administered on 1 of gestation days 8-12. Mice were sacrificed on gestation day 15, and dams were examined for weight gain and liver-to-body weight ratios; uterine contents of dams were also examined. Fetuses were weighed and examined for visceral and skeletal anomalies. Significantly greater numbers of maternal deaths occurred in treated mice, suggesting that 900 mg/kg is greater than the minimum lethal dose. Fetal deaths from treatment occurred at all times of administration, with the greatest effects observed on days 8 and 9 of gestation. Significantly greater gross malformations were induced in fetuses from all treatment groups over their untreated counterparts. Cleft lip, cleft palate, syndactyly, exencephaly, talipes and micromelia were commonly observed. Similar results were reported from a pilot study at 1000 mg/kg, but control data for the pilot study were not reported.

Willhite (1981) intravenously injected groups of five pregnant Golden hamsters on day 8 of gestation with 20, 50 or 100 mg/kg of the sodium salt of cacodylic acid. A group of seven pregnant hamsters injected with

distilled water served as a control. The 50 and 100 mg/kg doses induced some cranioschisis and abnormalities of ribs and kidneys, although the response did not occur in a dose-related fashion and statistical analysis was not performed.

6.5. OTHER REPRODUCTIVE EFFECTS

The Weed Science Society of America (1983) reported damage to spermatogonia cells in rats fed a diet that provided cacodylic acid at 226 mg/kg. No effects were observed at 118 mg/kg/day (see Section 6.1.2.1.). In the Nees (1960) study (see Section 6.1.2.1.), testicular pathological changes resulted when weanling rats were fed 280 mg/kg/day, but not 140 mg/kg/day for 20 days.

6.6. SUMMARY

Oral LD_{50} values in rats range from 644-1433 mg/kg, with little apparent age or gender difference in magnitude (see Table 6-1). Inhalation and intraperitoneal single exposure data indicate little difference in the sensitivity of rats compared with mice. Intraperitoneal LD_{50} values in both species ranged from 500-1000 mg/kg. In a 20-day dietary study in rats, testicular effects were observed at 180 mg/kg bw/day, but not at 140 mg/kg bw/day (Nees, 1960). A dietary concentration of 184 ppm was a NOEL in rats in a 30- to 90-day dietary study (Nees, 1968) and 30 ppm was a NOEL in a 90-day study in dogs (Derse, 1968). It is not clear whether the testis was examined in these longer-term studies.

Data regarding the toxicity of cacodylic acid in humans were not located; however, workers applying arsenic-containing silvicides had higher urinary concentrations of arsenic compounds, including cacodylic acid, than did nonexposed controls. The levels of cacodylic acid in the urine did not appear to rise with increased duration of exposure. Near normal levels were observed on Monday mornings.

Cacodylic acid did not yield evidence of carcinogenicity in an 18-month gavage/dietary exposure study, where mice were fed 46.4 mg/kg/day by gavage at days 7-28 of age and 121 ppm in the diet after day 28 of age (BRL, 1968; Innes et al., 1969). In a different BRL (1968) experiment with mice, a single subcutaneous injection at 464 mg/kg of cacodylic acid in distilled water did not produce a significant increase in tumor incidence compared with controls. A drinking water study produced equivocal evidence that cacodylic acid may promote liver tumors in partially hepatectomized rats initiated with DENA (Johansen et al., 1984). Results of mutagenicity testing were mixed. Tests in prokaryotes (Simmon et al., 1977; Jones et al., 1984; Andersen et al., 1972) and Drosophilia (Ramel and Magnusson, 1979; Valencia, 1981) were negative, but tests in Saccharomyces were positive (Simmon et al., 1977; Jones et al., 1984). Mixed results were obtained in various mammalian test systems (Simmon et al., 1977; Jones et al., 1984; Taylor et al., 1984). The compound is not scheduled for testing by the NTP (1988).

Developmental toxicity studies (Rogers et al., 1981; Kavlock et al., 1985; Chernoff and Kavlock, 1982) suggest that rats are more sensitive than mice. In a gavage study using rats, 40 mg/kg/day was associated with retarded maternal weight gain, reduced fetal body weights and retarded ossification (Rogers et al., 1981). An increased incidence of irregular palatine rugae was observed at 30 mg/kg/day. There were no significant effects at 15 mg/kg/day. In mice treated by gavage, 200 mg/kg/day resulted in adverse body weight effects on both the dam and the fetus; 400 mg/kg/day resulted in an increased incidence of cleft palate (Rogers et al., 1981).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

ACGIH (1987) recommended a TLV for arsenic and its soluble compounds of 0.2 mg As/m³, based primarily on the toxicity of As_2O_3 (ACGIH, 1986). OSHA (1985) has established a PEL for arsenic in air of 0.5 mg As/m³ TWA.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic life from exposure to cacodylic acid could not be located in the available literature as cited in Appendix A.

8. RISK ASSESSMENT

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential business information (CBI), which this document could not address, are not in existence. From examination of the bibliographies of the CBI data, however, it was determined that CBI data that would alter the approach to risk assessment or the risk assessment values presented herein do not exist.

8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the inhalation carcinogenicity of cacodylic acid could not be located in the available literature as cited in Appendix A.

8.1.2. Oral. In an 18-month study using (C57BL/6 x C3H/Anf)F1 (B6C3F1) and (C57BL6 x AKR)F1 (B6AKF1) strain mice, groups of 18 males and 18 females of each strain were administered gavage doses of 46.4 mg/kg bw/day in distilled water (an amount determined in a previous test to be a maximum tolerance level) from days 7-28. At day 28, adjustments were made for body weight changes, and a concentration of 121 ppm, which was calculated to deliver an equivalent daily dose, was added to the diet for the remainder of the 80-week test period. Eleven male and 18 female BC6C3F1 mice and 17 male and 16 female B6AKF1 mice lived until the end of the test. Although pulmonary adenoma, uterine leiomyoma and incidental lesions occurred in a few mice, no significant differences in incidence from those of untreated and pooled controls were noted.

8.1.3. Other Routes. Results were negative in another study (BRL, 1968) using the same strains of mice as above and in which single subcutaneous

injection of 464 mg/kg bw cacodylic acid in distilled water was administered in the nape of the neck to 28-day weanlings.

8.1.4. **Weight of Evidence.** Although only few animals of one species and one dose group were used in the above carcinogenicity studies, these studies are the best available data to date. The pre-determined MTDs of cacodylic acid were administered. The only additional pertinent information located in the literature was a possible tumor promoting effect of cacodylic acid when administered with DENA (Johansen et al., 1984). IARC (1980) concluded that there is inadequate support in the literature for the carcinogenicity of arsenic compounds in animals, and that evidence for such in humans is restricted to inorganic forms of arsenic. The lack of data regarding the carcinogenicity of cacodylic acid in humans and the inadequate studies in animals are the basis for assigning cacodylic acid to EPA Group D, not classifiable as to human carcinogenicity, using the U.S. EPA (1986a) classification scheme.

8.1.5. **Quantitative Risk Estimates.** The lack of positive data precludes estimation of carcinogenic potencies for cacodylic acid for either inhalation or oral exposure.

8.2. SYSTEMIC TOXICITY

8.2.1. **Inhalation Exposure.** Pertinent data regarding inhalation exposure to cacodylic acid could not be located in the available literature as cited in Appendix A.

8.2.2. **Oral Exposure.**

8.2.2.1. LESS THAN LIFETIME EXPOSURES (SUBCHRONIC) -- Toxicity studies of cacodylic acid are limited. A study by Nees (1960) regarding weanling rats and one reported in the Weed Science Society of America (1983) were both of inadequate duration for RfD determination (20 days and 3 weeks, respectively). A 90-day study of beagle pups (Derse, 1968) gave negative

results at the highest dose tested, 30 ppm, thus failing to establish a LOAEL or highest NOAEL.

The Nees (1968) 90-day study is marginally adequate for deriving an RfD. Weanling rats were fed cacodylic acid at dietary exposures of 0, 3, 15, 30 and 100 ppm for 30 or 90 days. There were no significant effects on body weight, food consumption, hematology, histology or organ weight at the highest concentration tested, therefore identifying a NOAEL of at least 100 ppm in the diet, equivalent to 5 mg/kg/day.

Additional data regarding the Nees (1968) study from the OPP CBI files indicated that the dietary concentrations presented actually refer to the arsenic equivalent rather than to cacodylic acid per se. Corresponding dietary concentrations of cacodylic acid are 0, 5.5, 27.6, 55.3 and 184 mg/kg. The highest dietary concentration corresponds to a dosage of 9.2 mg/kg/day, assuming that a rat consumes food equivalent to 5% of its body weight/day (U.S. EPA, 1980).

Application of an uncertainty factor of 300, 10 for interspecies extrapolation, 10 for variations within the human species and 3 to reflect limitations in the data base, results in an RfD for subchronic oral exposure of 0.03 mg/kg/day. Confidence in the study, data base and RfD are low.

8.2.2.2. CHRONIC EXPOSURES -- Pertinent data regarding chronic oral exposure to cacodylic acid could not be located in the available literature as cited in Appendix A. The OPP (1987) reports that chronic data are being generated. A provisional chronic oral RfD can be generated from the subchronic oral RfD of 0.03 mg/kg/day based on the NOEL of 9.2 mg/kg/day in the 90-day rat study by Nees (1968). Application of an uncertainty factor of 10 to the subchronic RfD of 0.03 mg/kg/day results in an RfD for chronic oral exposure of 0.003 mg/kg/day. A chronic oral RfD for cacodylic acid is currently under review by the U.S. EPA.

The boundaries for adverse effects and no effects are relatively unequivocal, enclosing a relatively small area of contradiction. The two LOAEL data points located on or within the area of contradiction are from the teratology rat study by Rogers et al. (1981). The point on the adverse effects line represents a slight teratological effect (irregular palatine rugae) in rats resulting from oral exposure to 30 mg/kg/day of cacodylic acid; the other (located above it) represents maternal toxicity (reduced weight gain) in the mouse that resulted from oral exposure to 200 mg/kg/day of cacodylic acid. These effect levels are clearly above the NOEL from Nees (1968) of 9.2 mg/kg/day, which has been chosen as a basis for subchronic and chronic oral RfD determination and to which uncertainty factors of 300 and 3000 have been applied, respectively (see above). The resulting subchronic and chronic RfD values (0.03 and 0.003 mg/kg/day, respectively) are well below the boundary for adverse effects.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The toxicity of cacodylic acid was discussed in Chapter 6 and dose-response data considered for CS derivation are summarized in Table 9-1. Since no chronic toxicity data were available, subchronic data were considered. Data suitable for RQ determination were provided by the staff of Rogers et al. (1981), who found teratogenic effects (cleft palates) in mice at an equivalent human dose of 30.2 mg/kg/day and teratogenicity in rats at an equivalent human dose of 5.1 mg/kg/day. The Weed Science Society of America (1983) reported atrophic changes in seminiferous tubules and decreased activity of spermatogonia in rats at an equivalent human dose of 38.6 mg/kg/day. CSs for these effects are presented in Table 9-2.

The effect chosen for RQ determination for cacodylic acid was teratogenicity in rats from the Rogers et al. (1981) study, which was the most sensitive yet reported. This effect yielded the highest CS (15.3), which corresponds to an RQ of 1000 (Table 9-3).

In another recent analysis, U.S. EPA (1987) derived candidate CSs for the teratogenic effects in rats and mice and also for the effects of maternal toxicity (reduced maternal body weight gain) in the dams treated for 10 days during gestation (Rogers et al., 1981). In recognition of the fact that the maternal effects observed were a manifestation of acute rather than chronic toxicity, an uncertainty factor of 100 was applied in the estimation of an equivalent human dose. This methodology appears to contradict that established by the Agency for the ranking of chemicals based on chronic toxicity data (U.S. EPA, 1984), in which it is stated that only subchronic and chronic data will be considered for derivation of CSs. Therefore, since in this analysis the acute manifestations of maternal toxicity observed

TABLE 9-1

Toxicity Summary for Cacodylic Acid

Route	Species/Strain	Sex	Number at Start	Average Weight (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Oral	weanling rats/ Sprague-Dawley	NR	NR	0.35[a]	food	77%	280 mg/kg for 20 days	280	not calculated[b]	Reduced activity of spermatogonia cells; atrophic changes in seminiferous tubules	Nees, 1960
Oral	weanling rats/ NR	NR	groups of 10, total number NR	0.35[a]	food	NR	226 mg/kg for 3 weeks	226	38.6[c]	Atrophic changes in seminiferous activity of spermatogonia	Weed Science Society of America, 1983
Oral/ gavage	rats/Albino CD	time-pregnant females	21-40	0.35[a]	distilled H_2O	99%	30 mg/kg/day, gestation days 7-16	30	5.1[c]	Developmental toxicity, irregular palatine rugae	Rogers et al., 1981
Oral/ gavage	mice/Albino CD-1	time-pregnant females	30-32	0.03[a]	distilled H_2O	99%	400 mg/kg/day, gestation days 7-16	400	30.2[c]	Developmental toxicity, retardation in weight and caudal ossification; cleft palates	Rogers et al., 1981
Oral/ gavage	mice/CD-1 random bred	pregnant females	20	0.03[a]	distilled H_2O	97%	1600 mg/kg on day 8 of gestation (single dose)	1600	not calculated[b]	Maternal toxicity; 20% mortality; reduced weight gain; developmental toxicity; reduced body weight; mortality, delayed ossification and renal papilla development	Kavlock et al., 1985

[a]Reference value from U.S. EPA (1986b) assumed.

[b]Values were calculated only for the lowest dose associated with a given effect.

[c]Calculated by multiplying the animal transformed dose by the cube route of the ratio of the animal body weight to the human body weight (70 kg).

NR = Not reported

TABLE 9-2

Composite Scores for Cacodylic Acid

Route	Species	Animal Dose (mg/kg/day)	Chronic Human MED[a] (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Oral/ gavage	mouse	400	2114	1.0	Developmental toxicity: cleft palates; feto-toxicity: retarda-tion in weight and caudal ossification	9	9	1000	Rogers et al., 1981
Oral/ feeding	rat	226	270.2[b]	1.9	Atrophic changes in seminiferous tubules; decreased activity in spermatogonia	6	11.4	1000	Weed Science Society of America, 1983
Oral/ gavage	rat	30	357	1.7	Developmental toxicity: irregular palatine rugae	9	15.3	1000	Rogers et al., 1981

[a]Calculated by multiplying the human equivalent dose by 70 kg to present the MED in terms of mg/day for a 70 kg human.

[b]The dose was divided by an uncertainty factor of 10 to approximate chronic exposure.

TABLE 9-3

Cacodylic Acid

Minimum Effect Dose (MED) and Reportable Quantity (RQ)

Route:	oral/gavage
Species/Sex:	Rat/female
Dose*:	357 mg/day
Duration:	gestation days 7-16
Effect:	Developmental toxicity: irregular palatine rugae
RV_d	1.7
RV_e	9
Composite Score:	15.3
RQ:	1000
Reference:	Rogers et al., 1981

*Equivalent human dosage

in developmental toxicity studies are not considered appropriate to use in derivation of a CS, the RQ derived here differs from that in U.S. EPA (1987).

9.2. BASED ON CARCINOGENICITY

Cancer studies were limited to long-term experiments which tested mice administered MTDs by the oral route (BRL, 1968; Innes et al., 1969) and by subcutaneous administration (BRL, 1968). Results of the studies were negative (see Section 6.1.). Although the sample sizes in these studies were small and were confined to one species (mice), they are the best studies available to date. Both IARC (1980) and U.S. EPA (1982) concluded that available data do not suggest that there is oncogenic risk. Cacodylic acid is categorized as an EPA Group D compound, not classifiable as to human carcinogenicity (U.S. EPA, 1986a).

Cancer study data for this compound are inadequate for calculating a Potency Factor. Therefore, since cacodylic is assigned to EPA Group D, it is given a no hazard ranking, and no RQ for cancer can be assigned.

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APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB
SCISEARCH
Federal Research in Progress

These searches were conducted in May, 1988, and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

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Grayson, M. and D. Eckroth, Ed. 1978-1984. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

APPENDIX B

Summary Table for Cacodylic Acid

	Species	Exposure	Effect	RfD or q_1^*	Reference
Inhalation Exposure					
Subchronic	ID	ID	ID	ID	NA
Chronic	ID	ID	ID	ID	NA
Carcinogenicity	ID	ID	ID	ID	NA
Oral Exposure					
Subchronic	rat	100 ppm arsenic, equivalent to 184 ppm cacodylic acid (9.2 mg/kg/day) in diet 90 days	none	0.03 mg/kg/day	Nees, 1968
Chronic	rat	100 ppm arsenic, equivalent to 184 ppm cacodylic acid (9.2 mg/kg/day) in diet 90 days	none	0.003 mg/kg/day	Nees, 1968
Carcinogenicity	ID	ID	ID	ID	NA
REPORTABLE QUANTITIES					
Based on Chronic Toxicity:		1000 pounds			Rogers et al., 1981
Based on Carcinogenicity:		ID			NA

ID = Insufficient data; NA = not applicable

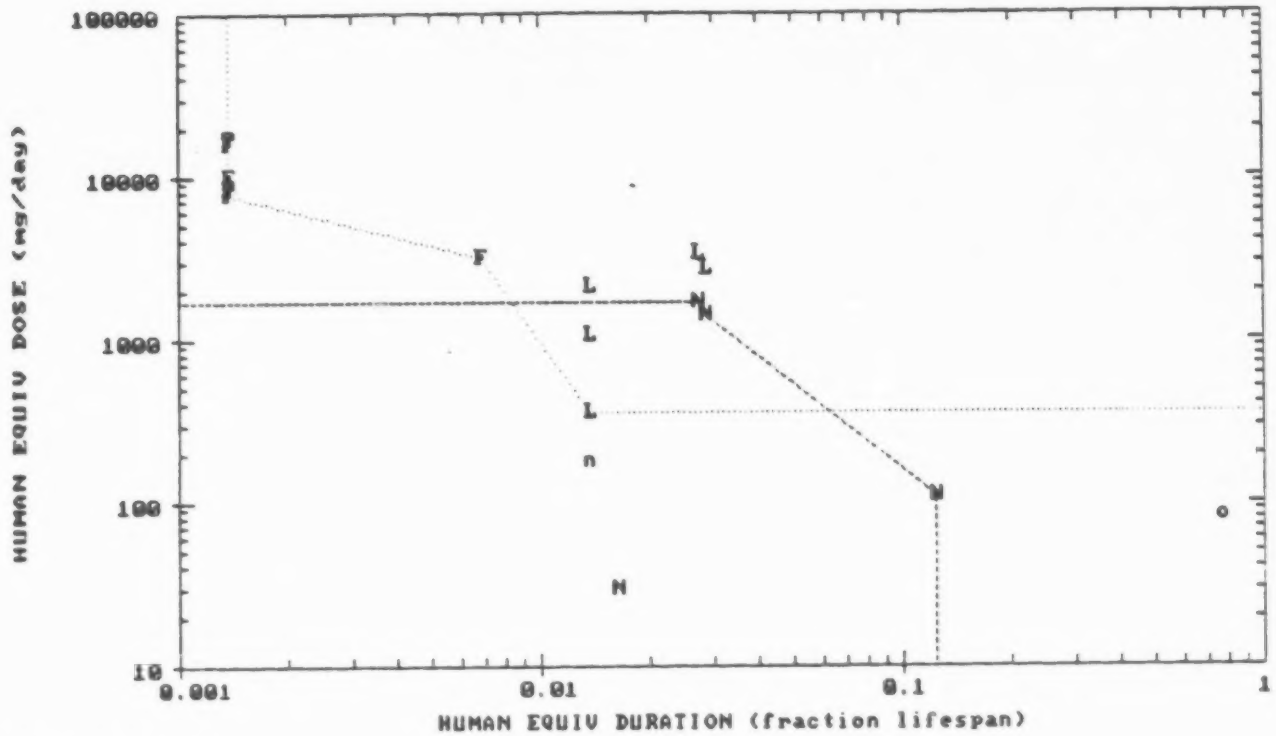
APPENDIX C

DOSE/DURATION RESPONSE GRAPH(S) FOR EXPOSURE TO CACODYLIC ACID

C.1. DISCUSSION

A dose/duration-response graph for oral exposure to cacodylic acid generated by the method of Crockett et al. (1985) using the computer software by Durkin and Meylan (1988) under contract to ECAO-Cincinnati is presented in Figure C-1. Data used to generate this graph are presented in Section C.2. In the generation of this figure all responses are classified as adverse (FEL, AEL or LOAEL) or nonadverse (NOEL or NOAEL) for plotting. If data are available for inhalation exposure: The ordinate expresses concentration in either of two ways. In figure(s) (---), the experimental concentration expressed as mg/m^3 was multiplied by the time parameters of the exposure protocol (e.g., hours/day and days/week) and is presented as expanded experimental concentration [expanded exp conc (mg/m^3)]. In figure(s) (---), the expanded experimental concentration was multiplied by the cube root of the ratio of the animal:human body weight to estimate an equivalent human or scaled concentration [scaled conc (mg/m^3)] (U.S. EPA, 1980; Mantel and Schneiderman, 1975).

The boundary for adverse effects (solid line) is drawn by identifying the lowest-adverse-effect dose or concentration at the shortest duration of exposure at which an adverse effect occurred. From this point an infinite line is extended upward parallel to the dose axis. The starting point is then connected to the lowest-adverse-effect dose or concentration at the next longer duration of exposure that has an adverse-effect dose or concentration equal to or lower than the previous one. This process is continued to the lowest-adverse-effect dose or concentration. From this point a line is extended to the right parallel to the duration axis. The region of adverse effects lies above the adverse effects boundary.



(Oral Exposure)

N = NOEL
n = NOAEL
L = LOAEL
F = FEL
o = NOCEL

FIGURE C-1

Dose/Duration-Effects from Oral Exposure to Cacocylic Acid:
Envelope Method

Source: Crockett et al., 1985

Using the envelope method, the boundary for no adverse effects (dashed line) is drawn by identifying the highest no-adverse-effects dose or concentration. From this point a line parallel to the duration axis is extended to the dose or concentration axis. The starting point is then connected to the next highest or equal no-adverse-effect dose or concentration at a longer duration of exposure. When this process can no longer be continued, a line is dropped parallel to the dose or concentration axis to the duration axis. The region of no adverse effects lies below the no-adverse-effects boundary. At both ends of the graph between the adverse-effects and no-adverse-effects boundaries are regions of ambiguity. The area (if any) resulting from intersection of the adverse-effects and no-adverse-effects boundaries is defined as the region of contradiction.

In the censored data method, all no-adverse-effect points located in the region of contradiction are dropped from consideration and the no-adverse-effect boundary is redrawn so that it does not intersect the adverse-effects boundary and no region of contradiction is generated. This method results in the most conservative definition of the no-adverse-effects region.

C.2. DATA USED TO GENERATE DOSE/DURATION-RESPONSE GRAPHS

Chemical Name: Cacodylic Acid
CAS Number: 75-60-5
Document Title: Health and Environmental Effects Document on Cacodylic Acid
Document Number: pending
Document Date: pending
Document Type: HEED

RECORD #1:

Species:	Rats	Dose:	1315.000
Sex:	Male	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	14.0 days
Route:	Gavage		

Number Exposed:	10
Number Responses:	5
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	9

Comment: LD_{50} value

Citation: Gaines and Linder, 1986

RECORD #2:

Species:	Rats	Dose:	644.000
Sex:	Female	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	14.0 days
Route:	Gavage		

Number Exposed:	10
Number Responses:	5
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	9

Comment: LD_{50} value

Citation: Gaines and Linder, 1986

RECORD #3:

Species:	Rats	Dose:	1433.000
Sex:	Both	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	14.0 days
Route:	Gavage		

Number Exposed:	10
Number Responses:	5
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	9

Comment: LD_{50} value for weanlings, both sexes

Citation: Gaines and Linder, 1986

RECORD #4:

Species:	Rats	Dose:	700.000
Sex:	NS	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	1.0 days
Route:	Oral (NOS)		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	9

Comment: LD_{50} value, details not available

Citation: Farm Chemical Handbook, 1987

RECORD #5:

Species:	Rats	Dose:	830.000
Sex:	Both	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	1.0 days
Route:	Oral (NOS)		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	9

Comment: LD_{50} value, details not reported

Citation: Weed Science Society of America, 1983

RECORD #6:

Species:	Rats	Dose:	1350.000
Sex:	NS	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	1.0 days
Route:	Oral (NOS)		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	9

Comment: LD_{50} value, details not reported

Citation: Bailey and White, 1965

RECORD #7:

Species:	Rats	Dose:	700.000
Sex:	Male	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	14.0 days
Route:	Gavage		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	9

Comment: LD_{50} value, incomplete description of study

Citation: Nees, 1960

RECORD #8:

Species:	Rats	Dose:	280.000
Sex:	NS	Duration Exposure:	20.0 days
Effect:	LOAEL	duration Observation:	20.0 days
Route:	Food		

Number Exposed:	10
Number Responses:	NR
Type of Effect:	ATROP
Site of Effect:	TESTE
Severity Effect:	7

Comment: Reduced activity of spermatogonia cells; atrophic changes in seminiferous tubules among weanlings.

Citation: Nees, 1960

RECORD #9:

Species:	Rats	Dose:	140.000
Sex:	Both	Duration Exposure:	20.0 days
Effect:	NOEL	Duration Observation:	20.0 days
Route:	Food		

Number Exposed:	10
Number Responses:	NR
Type of Effect:	ATROP
Site of Effect:	TESTE
Severity Effect:	3

Comment: Among weanlings, no histological effects noted on testes, brain, heart, lungs, abdominal organs or bone.

Citation: Nees, 1960

RECORD #10:

Species:	Rats	Dose:	9.200
Sex:	Both	Duration Exposure:	90.0 days
Effect:	NOEL	Duration Observation:	90.0 days
Route:	Food		

Number Exposed:	5
Number Responses:	NR
Type of Effect:	WGTDC
Site of Effect:	BODY
Severity Effect:	1

Comment: No effects noted on body weight, food consumption, organ weights, hematology. Unclear whether testis was examined.

Citation: Nees, 1968

RECORD #11:

Species:	Rats	Dose:	118.000
Sex:	N.S.	Duration Exposure:	3.0 weeks
Effect:	NOEL	Duration Observation:	3.0 weeks
Route:	Food		

Number Exposed:	10
Number Responses:	NR
Type of Effect:	ATROP
Site of Effect:	TESTE
Severity Effect:	1

Comment: No atrophic changes in seminiferous tubules or decrease in activity of spermatogonia cells.

Citation: Weed Science Society of America, 1983

RECORD #12:

Species:	Rats	Dose:	226.000
Sex:	N.S.	Duration Exposure:	3.0 weeks
Effect:	LOAEL	duration Observation:	3.0 weeks
Route:	Food		

Number Exposed:	10
Number Responses:	NR
Type of Effect:	ATROP
Site of Effect:	TESTE
Severity Effect:	7

Comment: Atrophy of seminiferous tubules, decreased activity of spermatogonia cells

Citation: Weed Science Society of America, 1983

RECORD #13:

Species:	Dogs	Dose:	0.750
Sex:	Both	Duration Exposure:	90.0 days
Effect:	NOEL	Duration Observation:	90.0 days
Route:	Food		

Number Exposed:	8	8
Number Responses:	NR	NR
Type of Effect:	ELIMI	ATROP
Site of Effect:	KIDNY	BODY
Severity Effect:	3	3

Comment: No effects noted on kidney or liver function, urinalysis, histopathology of major organs or tissues; unclear whether testes were examined.

Citation: Derse, 1968

RECORD #14:

Species:	Mice	Dose:	15.700
Sex:	Both	Duration Exposure:	80.0 weeks
Effect:	NOCEL	duration Observation:	80.0 weeks
Route:	Gavage		

Number Exposed:	18
Number Responses:	NR
Type of Effect:	CANCR
Site of Effect:	BODY
Severity Effect:	7

Comment: Incidence of pulmonary adenoma, uterine leiomyoma and incidental lesions was not significantly different from that of untreated and pooled controls

Citation: BRL, 1968; Innes et al., 1969

RECORD #15:

Species:	Rats	Dose:	15.000
Sex:	Female	Duration Exposure:	10.0 days
Effect:	NOAEL	Duration Observation:	21.0 days
Route:	Gavage		

Number Exposed:	21
Number Responses:	NR
Type of Effect:	TERAS
Site of Effect:	FETUS
Severity Effect:	3

Comment: No palatine effects noted in this teratology study. Dose administered on gestation days 7-16.

Citation: Rogers et al., 1981

RECORD #16:

Species:	Rats	Dose:	30.000
Sex:	Female	Duration Exposure:	10.0 days
Effect:	LOAEL	Duration Observation:	21.0 days
Route:	Gavage		

Number Exposed:	21
Number Responses:	NR
Type of Effect:	TERAS
Site of Effect:	FETUS
Severity Effect:	3

Comment: Teratogenic effects: irregular palatine rugae; dose administered on gestation days 7-16.

Citation: Rogers et al., 1981

RECORD #17:

Species:	Mice	Dose:	200.000
Sex:	Female	Duration Exposure:	10.0 days
Effect:	LOAEL	Duration Observation:	21.0 days
Route:	Gavage		

Number Exposed:	30
Number Responses:	NR
Type of Effect:	WGTIN
Site of Effect:	BODY
Severity Effect:	3

Comment: Maternal toxicity: reduced weight gain; dose administered on gestation days 7-16.

Citation: Rogers et al., 1981

RECORD #18:

Species:	Mice	Dose:	400.000
Sex:	Female	Duration Exposure:	10.0 days
Effect:	LOAEL	Duration Observation:	21.0 days
Route:	Gavage		

Number Exposed:	30
Number Responses:	1
Type of Effect:	TERAS
Site of Effect:	FETUS
Severity Effect:	3

Comment: Teratogenic effect: cleft palates in 57% of litters; dose administered on gestation days 7-16.

Citation: Rogers et al., 1981

RECORD #19:

Species:	Mice	Dose:			1600.000
Sex:	Female	Duration Exposure:			1.0 days
Effect:	FEL	Duration Observation:			18.0 days
Route:	Gavage				

Number Exposed:	20	20	20	20	20
Number Responses:	5	NR	NR	NR	NR
Type of Effect:	DEATH	WGTIN	dEATH	WGTIN	TERAS
Site of Effect:	N.S.	BODY	FETUS	FETUS	FETUS
Severity Effect:	9	3	9	3	3

Comment: Maternal and fetotoxicity (death, reduced weight gain); teratogenic effects (delays in ossification and renal papilla development; skeletal and soft tissue abnormalities markedly higher than controls

Citation: Kavlock et al., 1985

RECORD #20:

Species:	Mice	Dose:	3.400
Sex:	Female	Duration Exposure:	5.0 days
Effect:	FEL	Duration Observation:	17.0 days
Route:	Water		

Number Exposed:	24
Number Responses:	4
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	9

Comment: Maternal death; reduced fetal and maternal body weight gain

Citation: Chernoff and Kavlock, 1982

NR = Not reported